Synthesis and Characterization of Repeating Sequence Copolyesters

by

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Sequence in copolymers is underexploited in synthetic copolymer design despite the overwhelming evidence of the importance of sequence in controlling polymer properties that is seen in biological polymers. A series of poly(α-hydroxy acid)s consisting of lactic (L); glycolic (G) and caprolactone-derived (C) units has been prepared using segmer assembly polymerization (SAP). The segmers, which consist of the targeted repeat unit, e.g. LGC, are first prepared by the coupling of orthogonally protected building blocks. The periodic copolymers, e.g., $(LGC)_n$ were then prepared by a step-growth condensation reaction. The retention of the sequence in the copolymers was confirmed by NMR analysis and the chemical shifts were compared with those previously assigned based on the analysis of statistical copolymers. Thermal properties, T_g and T_m were found to depend both on composition and, in a few cases, sequence. Selected poly(lactic-*co*-glycolic acid)s (PLGAs) with embedded stereosequences (L_S vs. L_R), were found to form crystalline stereocomplexes, in some cases as blends and in others as homopolymers that included both stereoisomers as mini-blocks. The sequence fidelity of PLGAs was defined and determined for a series of copolymers with controlled levels and types of errors. Both NMR and Matrix-Assisted Laser Desorption/Ionization (MALDI) mass spectrometry were used to quantify the error level. An alternate synthetic method for sequenced PLGAs, based on Entropy-Driven Ring-Opening Metathesis Polymerization (ED-ROMP) was developed. Embedding the target

sequence in an unstrained macrocycle bearing an olefinic reactive group allowed for ED-ROMP and produced sequenced copolymers with improved molecular weight control relative to SAP. Kinetic studies were consistent with an entropy-driven process. Copolymers comprised of repeating sequences were synthesized by SAP and ED-ROMP and their properties were then characterized.

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LIST OF ABBREVIATIONS

Å	Ångstrom
AcOH	Acetic acid
atm	atmospheres
ATRP	Atom Transfer Radical Polymerization
B	Butenoic acid unit
Bn	Benzyl
C	ε-caprolactone derived 6-hydroxyhexanoic acid (caprolactic acid unit)
$CDCl_3$	Chloroform-d_3
CH_2Cl_2	Methylene chloride
COSY	Correlation spectroscopy
Đ	Dispersity
d	doublet
dt	doublet of triplets
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
DIC	N,N'-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribose nucleic acid
DP	Degree of polymerization
DPTS	4-(dimethylamino) pyridinium *p*-toluenesulfonate
DSC	Differential scanning chromatography
DVB	Divinylbenzene
ED-ROMP	Entropy-driven ring-opening metathesis polymerization
ED-ROP	Entropy-driven ring-opening polymerization
Eg	ethylene glycol
equiv.	Equivalents
ER	Error rate
errormer	PLGAs with controlled error rate
EtOAc	Ethyl acetate
G	Glycolic acid unit
g	Grams
Grubbs 2	Grubbs 2nd generation catalyst
h	hours

H_2	Hydrogen gas
Hed	Hexendioic acid unit
Hd	Hexandioic acid unit
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronculear multiple-quantum correlation spectroscopy
HRMS	High resolution mass spectrometry
Hz	Hertz
i	isotactic
J	coupling constant
kDa	kilodalton
L	L-lactic acid unit
L_{err}	Lactic acid error unit
L_{rac}	racemic lactic acid unit
L_R	D-lactic acid unit
L_S	L-lactic acid unit
M	Molar
m	multiplet
MALDI-ToF	Matrix-assisted laser desorption/ionization time of flight
MALLS	Multi angle laser light scattering
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
min	Minutes
mL	Milliliter
M_n	Number average molecular weight
mmol	millimoles
mol	moles
MS	Mass spectrometry
M_w	Weight average molecular weight
m/z	mass to charge
NMR	Nuclear magnetic resonance
Oed	Octendioic acid unit
Od	Octandioic acid unit
P	Pentenoic acid unit
Pd/C	Palladium on carbon
PDI	Polydispersity index
PGCA	Poly(glycolic-*co*-caprolactic acid)
PLA	Polylactide
PLCA	Poly(lactic-*co*-caprolactic acid)
PLGA	Poly(lactic-*co*-glycolic acid)
PLGCA	Poly(lactic-*co*-glycolic-*co*-caprolactic acid)
PDLA	Poly (D-lactide)
PLLA	Poly (L-lactide)
PS	Polystyrene
q	quartet
RCM	Ring-closing metathesis

ROP	Ring-opening polymerization
RSC	Repeating sequence copolymer
RT	Room temperature
s	Singlet
s	syndiotactic
SAP	Segmer assembly polymerization
SAXS	Small-angle x-ray scattering
SEC	Size exclusion chromatography
segmer	sequenced oligomer
SF	Sequence fidelity
SiR_3	*tert*-butyl-di-methylsilyl or *tert*-butyl-di-phenylsilyl
S/N	Signal to noise
TBAF	Tetra-butylammonium fluoride
TBDMS	*tert*-butyl-di-methylsilyl
TBDMSCl	*tert*-butyl-di-methylchlorosilane
T_g	Glass transition temperature
THF	Tetrahydrofuran
T_m	Melting transition temperature
WAXS	Wide-angle x-ray scattering
w_A	Weight fraction monomer A
w_B	Weight fraction monomer B
XRD	X-ray diffraction

PREFACE

I would like to begin by thanking and extending my deepest gratitude to everyone who has made it possible for me to be where I am today. Without my friends, family, and colleagues finishing my degree would not have been possible.

I would like to thank my advisor Dr. Tara Meyer for the countless hours and effort that she has spent on teaching me to be a better researcher and thinker. When I first came to Pitt I wanted to research the synthesis of natural products. I kind of fell into the field of polymer chemistry after taking a class on inorganic chemistry from Tara and heard her talk about her research one day. Joining Tara's group was probably one of the best choices I made during grad school. Ryan Stayshich was right when he said, "If you ever have to give bad news to Tara, show her a pretty NMR spectrum first!"

I would like to thank my many committee members Professors Nat Rosi, Toby Chapman, Kacey Marra, Alexander Star, and Seth Horne for taking the time out of their busy schedules. I would also like to thank the many people in the department who helped with my research over the years: Dr. Joel Gillespie for help with GPC, Sage Bowser and Dr. Damodaran Krishnan Achary for help with NMR, and Dr. Bhaskar Godugu for help with MALDI. To all of the group members that I have had the privilege of working with: Dr. Amy Short, Dr. Jian Li, Dr. Ben Norris, Mike Washington, Jeff Auletta, Shaopeng Zhang, Colin Ladd, Greg LeDonne, Xiao Jin,

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A lot of my time at Pitt was spent teaching in the undergraduate organic teaching labs. I discovered my love teaching and interacting with students during the many night labs that I had the pleasure of supervising. Drs. Ericka Huston and George Bandik are the *best* teaching mentors you could ever hope to have. I enjoyed the many hours I spent working (and chatting) with Ericka on the Chem 0340 manual. Always remember, “This is fine.” Every time a new group of grad students would arrive for orientation in the teaching organic labs, George would always tell the story about how he thought I hated him in the beginning of my time at Pitt. It took him a short time before realizing that I had a *somewhat* sarcastic sense of humor and we have been friends ever since.

I had an amazing group of friends while here at Pitt and without them I surely would have gone insane. Rob, Amy and Tim Short, Amsul, Tim, Joanne, and Gedi sharing laughs, our struggles and events such as the Lehigh Olympics will always be some of my fondest memories.

My family has been the one constant throughout my life and I love them more than they will ever now. Mom, Dad, and Phil thanks for always being there for me. Finally, to my best friend and wife Emily, meeting you was the best thing that ever happened to me. You have stuck by me for these past 11 years and I have loved every minute of it. Without you I wouldn’t be who I am today. We finally will be the Drs. Weiss.

1.0 INTRODUCTION

1.1 SYNTHESIS OF SEQUENCED COPOLYMERS

Nature has long been known to utilize sequence in biopolymers such as DNA and peptides. DNA contains an exact sequence of the monomers adenine, cytosine, guanine, and thymine. Peptides, on the other hand, are synthesized from a slightly larger pool of amino acids monomers (20). The exact sequence of monomers in these biomacromolecules gives rise to the overall three-dimensional structure as well as their functions and properties.[1-3]

While the relationship between sequence and properties is fairly well understood in the previously mentioned biopolymers, accessing exact sequences in synthetic copolymers is difficult to achieve. Recently, a push in the synthetic polymer community, including the Meyer group, has been undertaken to synthesize sequenced copolymers and study how their properties are affected by their monomer order.[4-9] In the last decade, our group has focused on synthesizing sequenced copolymers and investigating the interesting sequence specific behavior of these polymeric materials.[10-22]

This dissertation, which forms a part of this body of Meyer group contributions to the field of sequenced copolymers, is divided into five chapters. In Chapter 1 an overview of relevant background is presented, starting with the introduction of the importance of the polymers which are the subject of these studies, poly(lactic-*co*-glycolic acid)s (PLGAs), to the biomedical field.

Also described is the synthetic approach most widely used in the preparation of the random copolymers. Next, the methodology utilized by the Meyer group to synthesize Repeating Sequenced Copolymers (RSC)s by Segmer Assembly Polymerization (SAP) will be introduced.

In Chapter 2, the synthesis and characterization of RSCs of poly(lactic acid-*co*-caprolactic acid)s (PLCAs), poly(glycolic acid-*co*-caprolactic acid)s (PLGCAs), and the terpolymers poly(lactic-*co*-glycolic-*co*-caprolactic acid)s is discussed. The correlation between NMR and thermal data with sequence is analyzed.

In Chapter 3, the use of NMR spectroscopy and Matrix Assisted Laser Desorption/Ionization Time of Flight (MALDI-ToF) mass spectrometry to determine the sequence fidelity (and the error rate) in PLGAs is described.

In Chapter 4 a new synthetic strategy is presented for the preparation of sequenced poly(α-hydroxy acid)s. The method, Entropy-Driven Ring-Opening Metathesis Polymerization (ED-ROMP), produces polymers similar to those prepared by SAP but with improved molecular weight control.

In the last chapter the synthesis of enantiomeric PLGAs (polymers with opposite stereochemistry) and stereochemical mini-block copolymers (copolymers that contain short blocks of varying stereoisomers) is described. Evidence for the formation of sterereocomplexes is presented.

1.1.1 Poly(lactic-*co*-glycolic acid)s: importance as a material in biomedical applications

Poly(α-hydroxy acid)s such as PLA, poly(ε-caprolactone) (PCL), poly(glycolide) and their copolymers (particularly PLGA), have been used in applications such as drug delivery and tissue engineering scaffolds.[23-28] The polymers are biodegradable and bioassimilable once they have

been hydrolytically degraded into their corresponding monomeric units. Stereochemically pure PLA, PCL, and PGA are generally highly crystalline materials which yield longer degradation times so the body takes longer to clear the materials from the body.[23,26,29] Of these biodegradable polymers, PLGAs, which comprise random polymers of lactic acid (L) and glycolic acid (G), have dominated due to their faster degradation rates and overall lack of crystallinity.[23,24,27] These properties have translated into the widespread use of PLGAs in biomedical applications.[23-25,30] Although these polymers, as used are random copolymers, the overall properties of PLGA can be tuned by varying the polymer's molecular weight, the L:G content of the polymer, the stereochemistry of the lactic unit, and the average block length if the L and G units.[23-25]

PLGAs are generally synthesized using one of two methods. The first is the step-wise condensation polymerization of glycolic acid and lactic acid.[31-33] The second, and by far the most widely used, is the ring-opening polymerization (ROP) the cyclic lactones, lactide and glycolide (**Figure 1**[22]).[34-39] Both of these approaches produce random sequences of the monomers L and G. In general, the only sequence that can be obtained using these methods is the simple alternating sequence, which can be accessed by ROP of the difficult-to-prepare methyl glycolide.[36-38,40]

It has been our goal, to develop methods for preparing sequenced PLGAs so that we can explore the connection between sequence and properties, with the long term objective of preparing novel materials for bioengineering applications.

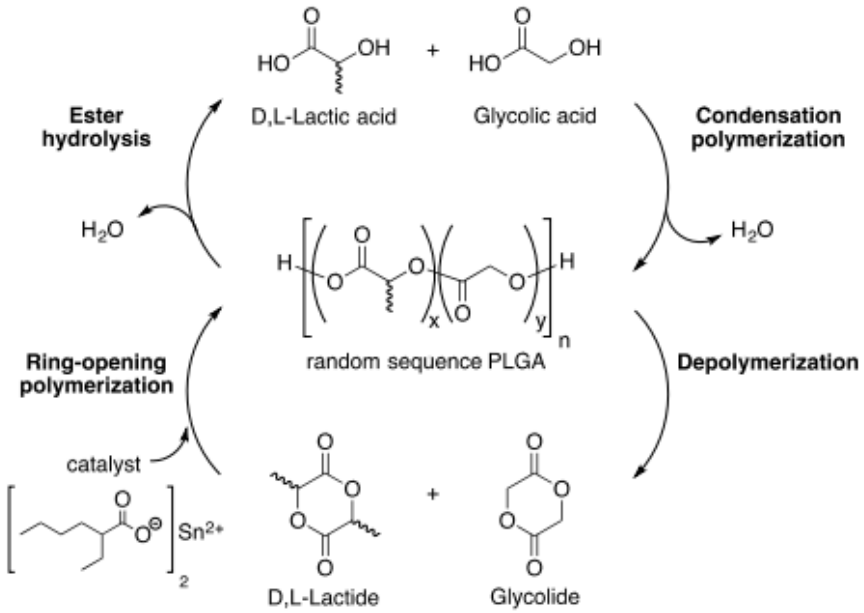


Figure 1. The synthesis of PLGA by condensation and ring-opening polymerization. *Reprinted and modified with permission Ref. 22,* Short, A. L., "Sequenced copolymers with controlled molecular weights prepared via entropy-driven ring-opening metathesis polymerization" University of Pittsburgh, 2016. C*opyright 2016 Amy L. Short.*

1.1.2 Sequenced copolymers and their preparation

Nature uses sequence, or ordering of specific monomers, in biomacromolecules such as DNA and proteins to dictate structure and function.[1-3,41,42] While the importance of sequence has been known for decades, sequence in synthetic materials has been relatively under utilized.[5-9,43] Creating polypeptides with an exact sequence was investigated early on by Vigneaud *et al.* where an octapeptide with the hormonal activity of oxytocin was synthesized[44] and revolutionized by R. B. Merrifield when solid phase synthesis of peptides was developed.[45]

Until recently, there has been little to no control over sequence in synthetic copolymers. Alternating, gradient, and block copolymers were some of the the first steps towards creating synthetic sequenced copolymers.[46-50]

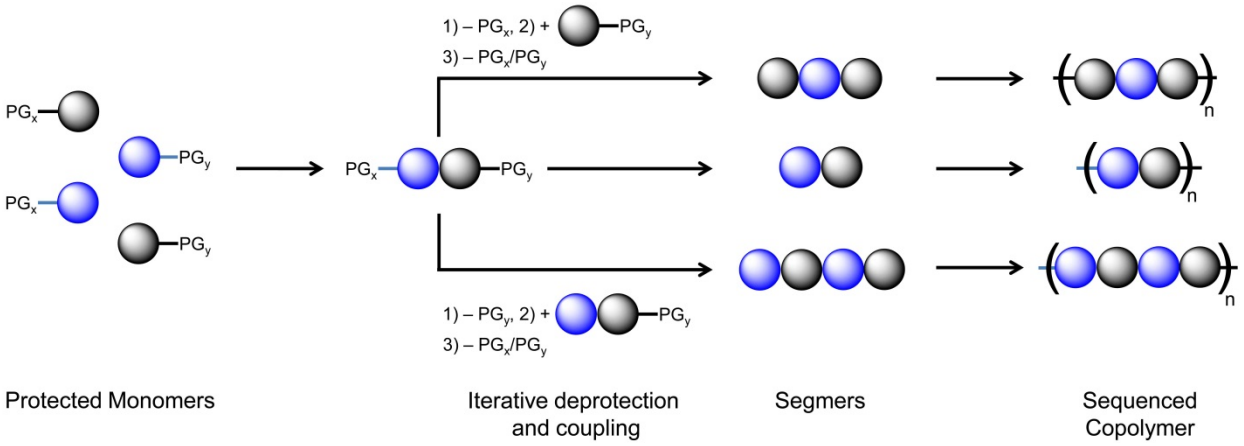
More recent attempts at sequenced materials have utilized a variety of methodologies to create highly orderd polymers. Chain-growth polymerizations have been utilized by various groups for the synthesis of precision polymers.[51-53] Using atom transfer radical polymerization (ATRP), the Matyjaszewski group has been able to synthesize block, gradient, and periodic copolymers.[54]

Sequenced copolymers have also been prepared by using step-growth mechanisms.[53,55-61] The Meyer group has also a developed a step-growth polymerization methodology to synthesize sequenced copolymers (described in the next section).

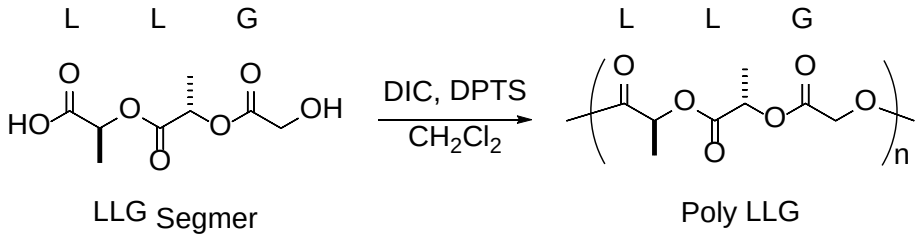
Taking a page from Nature, sequenced copolymers have been prepared using templates.[62-65] DNA and synthetic templates have been developed to direct polymerization and obtain sequenced copolymers.

1.1.3 Repeating sequence copolymers prepared via segmer assembly polymerization

The Meyer group has developed what we have termed the Segmer Assembly Polymerization (SAP) method to polymerize precisely sequenced oligomers (segmers) of lactic and glycolic acid. PLGAs prepared by SAP consist of a periodic repeat of the target sequence. The segmers are prepared by coupling reactions of orthogonally protected monomers (**Scheme 1**). Upon full removal of the protecting groups the segmers are polymerized using a condensation polymerization method to give repeating sequence PLGA (**Scheme 2**). More complex sequences can be obtained by the iterative deprotection and subsequent coupling reactions to other monomers. We have demonstrated that this approach can be used to form polymers with a large variety of embedded sequences.[14-17]



Scheme 1. SAP methodology of iterative deprotection/coupling reactions to prepare segmers. Segmers are then polymerized to to give a repeating sequence copolymer.



Scheme 2. Segmer assembly polymerization of the segmer **LLG** (contains a lactic unit connected to another lactic unit and a glycolic unit) to yield a repeating sequence copolymer of **Poly LLG**.

Using this approach, Ryan Stayshich *et al.*, prepared the first examples of sequenced PLGA copolymers. The M_ns of the polymers ranged from 12-41 kDa with dispersities (Đ) between 1.3 and 1.6. ^{1}H NMR spectroscopy of the sequenced copolymers showed that solution-phase conformations of the PLGAs were highly sequence and stereochemically dependent. The high resolution obtained in the NMR spectra proves that polymers synthesized have an exact sequence with little to no scrambling.[15]

Hydrolysis studies on these polymers conducted by Li *et al.* provide evidence that sequence has a dramatic effect on the degradation profiles of sequenced PLGAs. They compared the hydrolysis rate of random PLGAs prepared by ROP, and the SAP method (polymerization of LL, LG, GL, and GG oligomers) and two alternating **Poly LG**s with different molecular weights. The random PLGAs exhibited rapid mass loss in the first two weeks. The sequenced PLGAs

displayed a more linear hydrolysis rate after an initial small mass loss. This linear rate is dramatically different than that of the random PLGAs showing that sequence in the alternating polymers did in fact have an effect on the polymer's properties.[18-20]

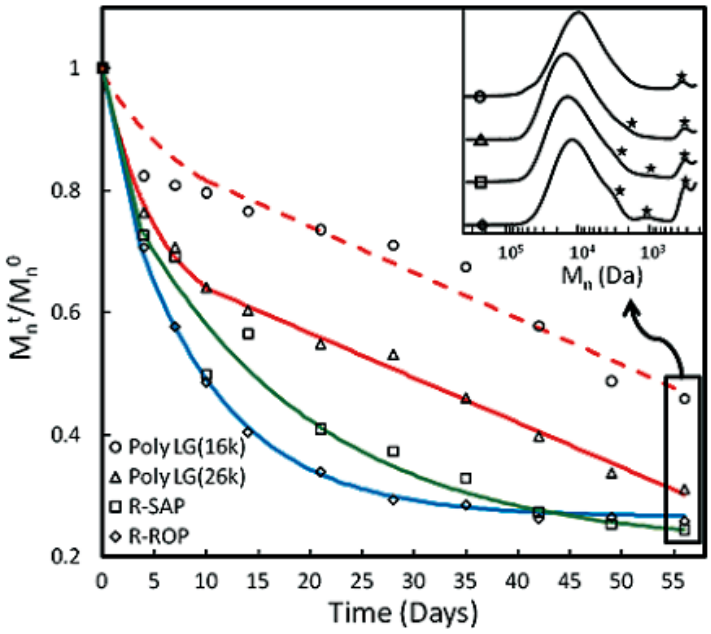


Figure 2. Plot of normalized molecular weight as a function of time for the repeating sequence and random copolymers of poly(lactic-coglycolic acids). Inset: SEC plots for day 56 hydrolysis samples. Asterisks represent low-molecular-weight oligomers. *Reprinted with permission from Ref 18, Li, J.; Stayshich, R. M.; Meyer, T. Y. "Exploiting Sequence To Control the Hydrolysis Behavior of Biodegradable PLGA Copolymers" J. Am. Chem. Soc. 2011, 133, 6910. Copyright 2011 American Chemical Society.*

While the RSCs of PLGA displayed sequence-dependent properties over their random counterparts, the SAP methodology did not allow us to have molecular weight control of our polymer samples since it is a condensation polymerization. Without molecular weight control, repeating the same polymerization of a segmer will not necessarily yield a polymer with the same molecular weight as a previous experiment. Since polymer properties are to an extent dependent on molecular weight,[66] there was an obvious need to develop a method that would allow for the synthesis of sequenced PLGAs with molecular weight control.

1.1.4 Entropy-driven ring-opening polymerization

We hypothesized that entropy-driven ring-opening polymerization (ED-ROP) might be a useful method to take a step closer to synthesizing sequenced copolymers with molecular weight control. ED-ROP, while very similar to ROP, has a few characteristics that set it apart from the the common ROP. ROP generally involves macrocycles that consist of 5-8 atoms and the driving force of the reaction is the release of ring strain, an enthalpic process. When the ring size becomes too large, around 14 atoms or larger, the enthalpic payoff is no longer significant enough to drive the reaction. The polymerization mechanism becomes that of ED-ROP. Upon ring-opening, the new conformational freedom of the atoms increases, the entropy of the reaction increases driving the reaction forward.[67]

ED-ROP takes advantage of the equilibrium between linear and cyclic species, the ring-chain equilibrium. When in dilute solutions the equilibrium favors cyclic species, while in concentrated solutions the chain or polymer is favored. This polymerization mechanism is neither a step-growth nor a chain-growth process due to this equilibration process and has a theoretical Đ of 2.[68] The molecular weight of the polymers produced will depend on the amount of end-groups that are introduced to the system. In many instances, a catalyst will be used for ED-ROP and the catalyst is the source of the end-group. This allows the degree of polymerization (DP) to be predicted based on the monomer to catalyst ratio.[67,68]

ED-ROP can occur via multiple mechanisms; some examples are anionic, coordination-insertion, and ring-opening metathesis polymerization (ROMP). Poly(alkylesters) have been prepared by all three of these mechanisms.[68] Of particular importance is the polymerization method of entropy-driven ring-opening polymerization (ED-ROMP). ED-ROMP will be discussed in Chapter 4, where it was utilized in the synthesis of sequened PLGA analogues.

2.0 SYNTHESIS OF REPEATING SEQUENCE COPOLYMERS OF LACTIC, GLYCOLIC AND CAPROLACTIC ACIDS

Sections 2.2 – 2.5 of this chapter have been reproduced and modified with permission from Weiss, R. M.; Jones, E. M.; Shafer, D. E.; Stayshich, R. M.; Meyer, T. Y., "Synthesis of Repeating Sequence Copolymers of Lactic, Glycolic and Caprolactic Acids" *J. of Polym. Sci. Part A: Polym. Chem*. **2011**, *49*, 1847-1855.[17]

2.1 INTRODUCTION

Sequence control in synthetic copolymers beyond simple alternation or the deliberate incorporation of long blocks is rare despite Nature's spectacular examples of the potential benefits to be derived from strict control of polymer composition e.g. DNA and functional enzymes. Inspired by the sequence-derived properties of these biopolymers, however, there is an increasing interest in exploiting monomer order to tune polymer properties.[5,6,41,69-73]

One area of potential application for sequenced copolymers that is particularly compelling is the creation of tailored biodegradable polyesters suitable for *in-vivo* uses such as tissue engineering scaffolding and drug-delivery. The most important class of polymers used for these

purposes are random copolymers prepared by ring-opening polymerization (ROP) of lactide, glycolide and other strained lactones.[26,30,39,74-80] While the properties of these polyesters match well to the requirements in many cases, it is challenging to optimize them for specific applications since they are random copolymers of a necessarily limited list of bioassimilable monomers. The introduction of sequence control in these materials would greatly increase the range and control of properties without introducing new potentially toxic monomers or derivatives.

Recently our group has reported the synthesis of repeating sequence copolymers (RSCs) of glycolic and lactic acids (PLGAs).[14,15] In the current study, we expand our polyester family to include caprolactic acid, the third most common monomer in this class of degradable polyesters. The expansion not only allows us to exploit the specific properties of this more flexible unit, which has been found to lower thermal transition temperatures (T_g and T_m) and increase tensile strength/elasticity of copolymers relative to PLGAs,[81] but also to create and investigate more complex ternary sequences. Herein, we describe the preparation and basic characterization of a family of sequenced copolymers bearing glycolic and caprolactic units (PGCAs), lactic and caprolactic units (PLCAs), and glycolic, lactic and caprolactic units (PLGCAs).

2.2 RESULTS AND DISCUSSION

2.2.1 Naming conventions

For simplicity, monomers, segmers and polymers will be named according to the following conventions. Using the abbreviations in **Table 1**, segmers are represented by listing the

monomers in sequence order starting from the carboxylic acid end. The monomer 6-hydroxyhexanoic acid is referred to throughout this paper by the less commonly used name of caprolactic acid and is represented with the letter C to be consistent with the literature on the closely related polymers involving the ROP of Ɛ-caprolactone. The terminal groups of oligomers are specified in the case where the acid and/or alcohol end-groups are protected. Using this approach, the name Bn-LLC-SiR_3 describes a trimeric segmer composed of a benzyl protected S-lactic acid, another S-lactic unit, and a silyl protected caprolactic unit. Polymer names are derived simply from the sequence used in their preparation: the polymer of deprotected oligomer LLC is termed for example, poly LLC. Note that the polymer name reflects the exact segmer used in the synthesis. It should be understood, however, that the names poly LLC and poly LCL would describe a polymer with the same repeating sequence overall, …LLCLLCLLCLLCLLCLLC…; the only differences would be in the identities of the terminal units.

Table 1. Naming conventions for the segmers and polymers.

Symbol	Definition
C	Caprolactic (6-hydroxyhexanoic) acid unit
G	Glycolic acid unit
L	Lactic acid unit with *S*-stereochemistry (L-lactic acid)
$\mathbf{L}_{\boldsymbol{R}}$	Lactic acid unit with *R*-stereochemistry (D-lactic acid)
$\mathbf{L}_{\boldsymbol{rac}}$	Lactic acid unit with a mixture *S and R* stereochemistry
Bn	Benzyl protecting group
$\mathbf{SiR_3}$	Silyl protecting group (*tert*-butyldimethylsilyl)

2.2.2 Synthesis of sequenced copolymers containing L, G, and C

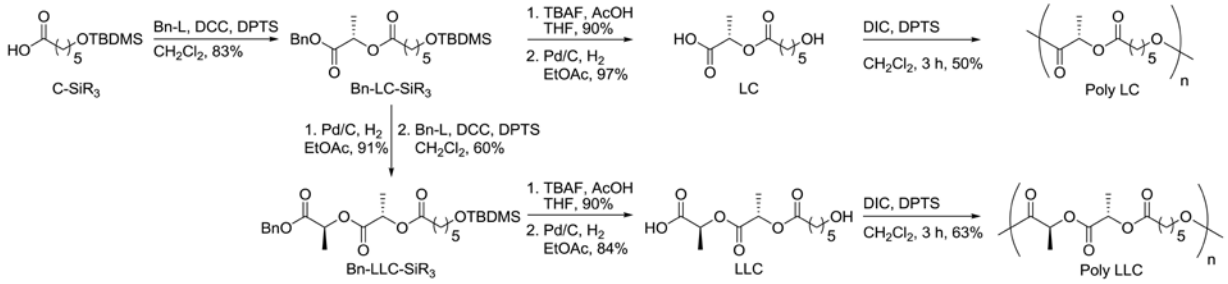
The diprotected dimers, **Bn-CC-SiR$_3$**, **Bn-GG-SiR$_3$**, **Bn-GC-SiR$_3$**, and **Bn-LC-SiR$_3$**, were assembled in good yield with N,N'-dicyclohexylcarbodiimide/4-(dimethylamino)pyridinium *p*-toluenesulfonate (DCC/DPTS) coupling of orthogonally protected monomeric building blocks consisting of the benzyl protected acids (**Bn-L**, **Bn-L$_R$**, **Bn-L$_{rac}$**, **Bn-G**, **Bn-LL** and **Bn-C**) and silyl protected alcohols (**C-SiR$_3$** and **G-SiR$_3$**), which were synthesized as previously reported.[14,15,59,60] Longer, more complex sequences were assembled by selective deprotection and subsequent coupling of monoprotected units. *tert*-butyldimethylsilyl (TBDMS) groups were removed by reaction with acetic acid buffered tetrabutylammonium fluoride in THF. The orthogonal benzyl protecting groups were removed by hydrogenolysis in EtOAc with 10% Pd/C (5% w/w) under 1 atm H_2.

Repeating sequence copolymers of C, G, and L were synthesized from the completely deprotected segmers in yields from 40-85% (**Table 2**) using N,N'-diisopropylcarbodiimide (DIC) and DPTS to promote coupling (**Scheme 3**, poly LC and poly LLC examples).[82] Polymers were characterized by NMR spectroscopy, size exclusion chromatography (SEC) and differential scanning calorimetry (DSC). Although transesterification was not significant as shown by analysis of ^{1}H NMR spectra, resonances for small amounts of N,N'-diisopropylurea, produced as a by-product of the polymerization, were observed in some samples. The complete syntheses for all segmers are available in section 2.5.

Table 2. PLGCA RSC Characterization

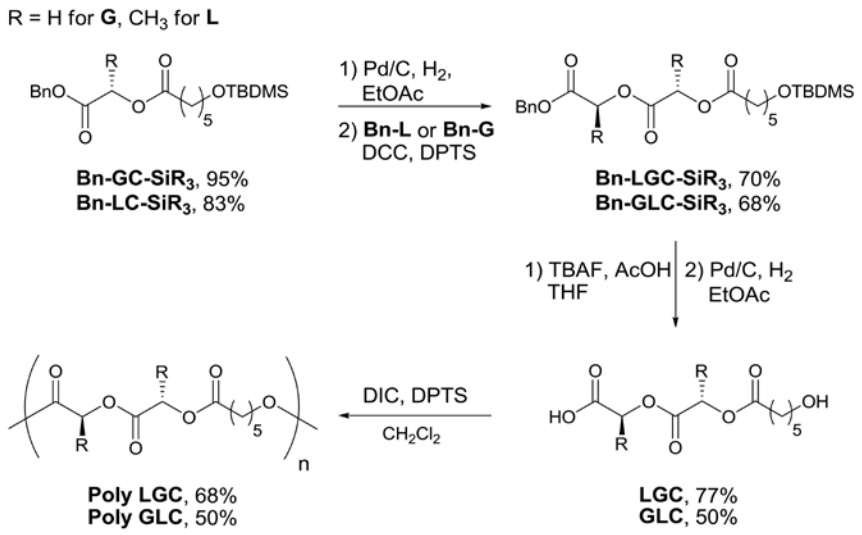
Polymer	Building Blocks	% Yield Polymer	M_n[a] (kDa)	Đ[b]	DP[c]	T_g[d] (ºC)	T_m[f] (ºC)
LC	L+C	50	37.9	1.4	204 (408)	-29.6	32.9
LLC	L+LC	63	30.8	1.4	119 (357)	-7.7	---
L$_R$LC	L$_R$+LC	40	30.7	1.4	111 (333)		---
L$_{rac}$LC	L$_{rac}$+LC	58	25.7	1.3	93 (279)		---
CLC	C+LC	43	26.9	1.4	90 (270)	-45.4	2.7 (34.2)[g]
LLCC	L+(L+CC)	67	40.6	1.6	109 (436)	-26.8	---
LLLC	LL+LC	59	24.0	1.5	73 (292)	5.7	---
LLLLC	L+(LL+LC)	67	35.8	1.4	89 (445)	17.9	---
LLCLC	L+(LC+LC)	73	49.1	1.4	110 (550)	-19.8	---
GC	G+C	57	26.4	1.4	153 (306)	-37.6	35.6 (64.3)[g]
GGC	G+GC	72	24.9	1.5	108 (324)	-19.8	36.5 (43.0)[g]
CGC	C+GC	56	18.3	1.4	64 (192)	-49.7	45.4
GGCC	GG+CC	85	33.8	1.6	98 (393)	-36.0	41.3
GGGC	G+(G+GC)	83	22.4	1.4	78 (311)	-8.3	53.1 (67.3)[g]
GGCGC	G+(GC+GC)	65	21.7	1.5	54 (270)	-30.1	34.2
LGC	L+GC	68	27.3	1.5	112 (336)	-16.2 (-17.1)[e]	---
GLC	G+LC	50	29.4	1.4	120 (360)	-10.5 (-9.4)[e]	37.7
GCLC	GC+LC	51	20.6	1.4	57 (228)	-34.4	---

a) Determined by SEC in THF relative to PS standards. b) M_w/M_n. c) Based on oligomer weight. (Based on monomer molecular weight). d) Obtained in second heating cycle at 10ºC a min. e) Annealed on the DSC, cooling 0.2 ºC/min. f) Obtained in first heating cycle at 10ºC a min. g) Values in parenthesis denotes a second T_m.



Scheme 3. Synthesis of example repeating sequence copolymers of lactic and caprolactic acids (**poly LC** and **poly LLC**).

We have prepared 18 RSCs comprising a variety of permutations: dimeric (LC, GC); trimeric (LLC, L$_R$LC, L$_{rac}$LC, CLC, GGC, CGC, <u>LGC</u>, <u>GLC</u>); tetrameric (LLCC, LLLC, GGCC, GGGC, <u>GCLC</u>); and pentameric (LLLLC, LLCLC, GGCGC). Of these combinations 15 are binary combinations of either C + L or C + G and three are ternary such that all three monomers are present, C + G + L (ternary sequences are underlined). Of particular interest are the sequences LGC and GLC which are connective isomers with identical compositions (**Scheme 4**).



Scheme 4. Synthesis of example repeating sequence copolymers of poly LGC and poly GLC.

The molecular weights of the polymers are moderate but respectable, given that the polymerization proceeds via a step-growth condensation mechanism. The M_ns of the polymers range from 18-49 kDa, with an average of 29 kDa (THF, PS standards). The dispersities (Đ) are narrow (1.3-1.6). MALLS analysis of sequenced copolymers of the closely related PLGA series acquired in an earlier study suggest that the absolute molecular weight of these polymers is 50-90% of the SEC weight, depending on sequence.[15] Based on this comparison and the lack of visible end groups in the NMR spectra we can conclude that the absolute molecular weights for even the shortest polymers reported here are greater than 10 kDa and that the monomer unit-based DPs are greater than 100.

2.2.3 NMR analysis of sequenced copolymers containing L, G, and C

The NMR data for all of the copolymers were analyzed in detail and by comparing these data with our absolute knowledge of the monomer sequences we have been able to unambiguously

assign shifts for a variety of local monomer environments. Prior to presenting the analysis, however, it is important to describe the spectral conditions and to clarify the conventions of representation that we use to label local sequences. NMR data were generally acquired in $CDCl_3$ except for the ^{13}C NMR spectra of the polymers containing only C and G monomers which were also analyzed in DMSO-d_6 at 86 ºC to provide a more direct comparison with literature data for the random analogues.

It is also important to standardize the order of representation of the sequences. As expressed previously, our convention is to write sequences from the carboxylic acid terminus to the alcohol end. The importance of rigorously adopting this convention is illustrated by the comparison of the two sequences **CLL<u>C</u>CLLC** and **CLLC<u>C</u>LLC**. In both sequences, the underlined caprolactic unit has both a C and an L closest neighbor. For **CLL<u>C</u>CLLC**, however, the L neighbor is on the carboxyl side and the C neighbor is on the alkoxy side. For **CLLC<u>C</u>LLC** the relationships are reversed. This difference results in a unique chemical environment for each of the caprolactic units as can be seen in the ^{13}C NMR carbonyl shifts of δ 172.8 and δ 173.4, respectively (*vide infra*). As these two sequences are appear palindromic, however, it is crucial to the correct assignment that there is no ambiguity in the directionality of the sequence as written.

To further the understanding of structure and function for polyesters bearing caprolactic units we have prepared exact sequence copolymers and have been able by in-depth analysis to *independently* assign the shifts of particular sequences and to more definitively determine the sensitivity of those shifts to the identity of the neighboring units. At the most basic level we can unambiguously assign the ^{13}C carbonyl NMR resonances for the C, G and L units in all sequences by chemical shift (**Figure 3**). Caprolactic carbonyls fall in the range of δ 173.43-172.58, lactic carbonyls δ 170.85-169.55, and glycolic carbonyls δ 167.87-166.59. In order to

discuss the assignment of resonances by sequence in more detail, however, it is important to note that the polymerization of a particular segmer produces multiple potential sequence patterns depending on the number of neighbors considered. **Poly CLC**, for example, has three spectroscopically distinct monomers since the C's are inequivalent. Each of those monomers sits in a sequence environment that can be described in terms of the number of neighbors that significantly affect the shift. These patterns are illustrated in **Figure 4** and are represented by the code "#_#", where # represents the number of neighboring units on each side that contribute to the observed shift.

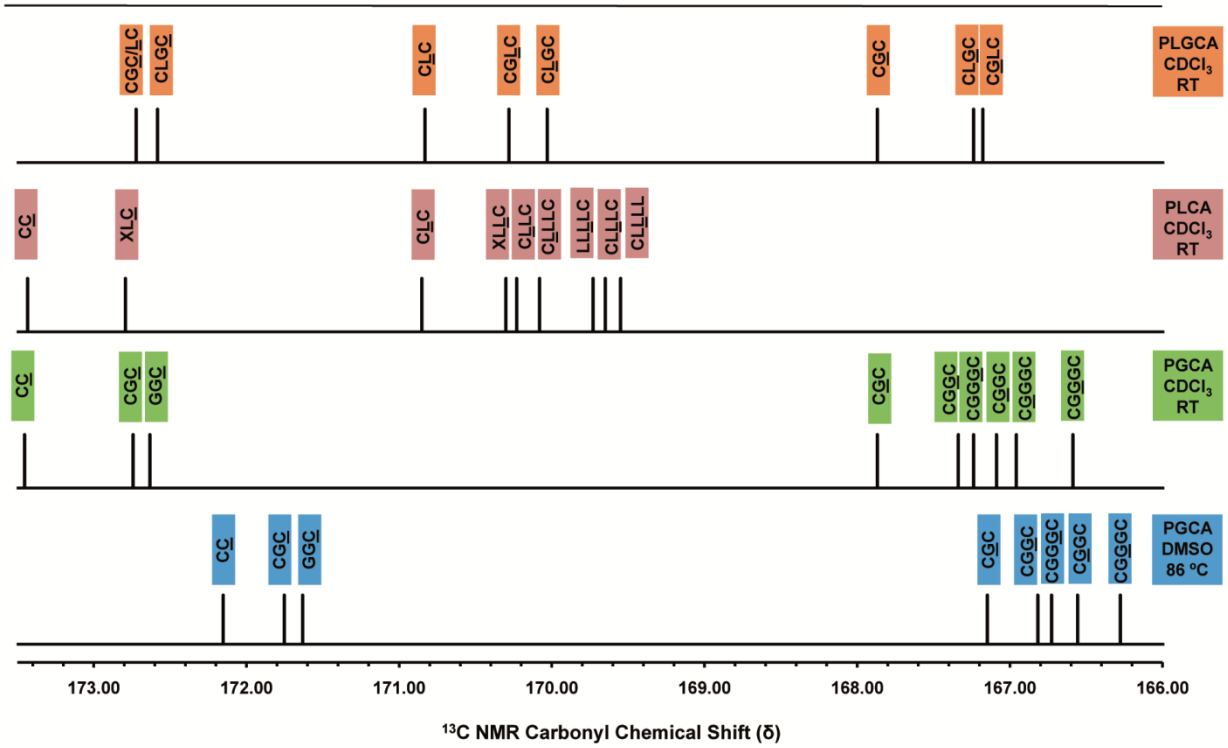


Figure 3. Composite figure overlaying the ^{13}C NMR chemical shifts for the carbonyls from all sequences within the prepared RSCs for three copolymer families listed bottom to top: (blue) PGCA in DMSO-d_6 at 86 ºC, (green) PGCA in $CDCl_3$ at RT, (pink) PLCA in $CDCl_3$ at RT, and (orange) PLGCA in $CDCl_3$ at RT. X denotes that the shift is the same if either an L or a C is located in that position.

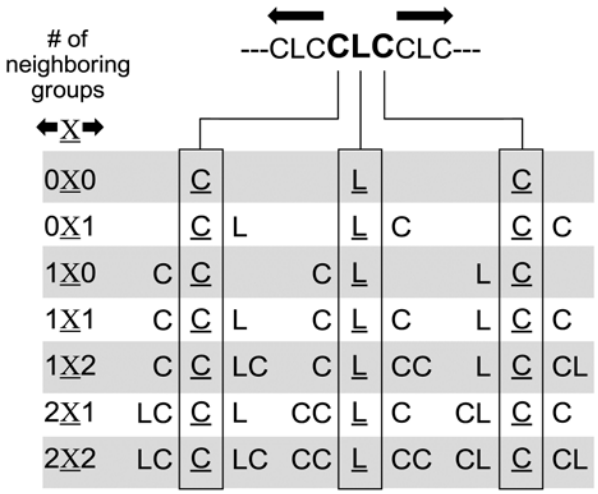


Figure 4. Sequence environments for each monomer in **poly CLC**. The range of possible sensitivities is expressed by truncation of the sequence to those units that contribute e.g. CCLC and represented generically by the notation #X#, where X is the monomer whose shift is being analyzed and # represents the number of neighbors affecting the ^{13}C chemical shift of the carbonyl of the sequence e.g. 1X2.

By comparing the chemical shifts of polymers bearing overlapping sequences we have been able to determine the degree of sensitivity for the carbonyl resonances of particular units to their neighbors. In the PLCA family, for example, the chemical shift of a lactic unit surrounded by two caprolactic units i.e. CLC is sensitive only to the 1_1 level. The identity of the next neighbors outward does not change the chemical shift; the lactic carbonyl of CCLCC exhibits the same chemical shift as LCLCL. In contrast, an L unit of a PLCA surrounded by two L units will be sensitive to a 2_2 level of resolution; the lactic carbonyls of LLLLC, CLLLC, and CLLLL all have distinct chemical shifts.

By comparing the spectra across the different families, larger trends in resolution sensitivity can be identified. In particular, we observe that the chemical shifts for the carbonyl units flanked by caprolactic units are generally insensitive to further neighboring groups. For example, the shift of CLC, which corresponds to a 1_1 relationship, is found at δ 170.85 in **poly LC**, **poly CLC**, **poly LLCLC**, and **poly GCLC**. Although the CLC subunits in these polymers have inequivalent sequences when the next nearest neighbors are considered, there is no difference in

carbonyl shift. The C units themselves were also found to be only mildly sensitive to neighbor identity in several sequences such as C<u>C</u>, CG<u>C</u>, and L<u>C</u>. The chemical shift was found to depend primarily on the identity of the monomer or monomers located to the left using the C-O convention. The flexibility and increased chain length of the caprolactic unit relative to the G and L units is the most probable reason for the observed attenuation of the influence of the neighboring groups on chemical shift overall.

Previously, our group has studied the effects of varying the stereochemistry of lactic acid units in RSCs of PLGAs.[15] To continue this study with the PLCA sequences, two copolymers **poly L*R*LC** and **poly L*rac*LC** (where L_R contains the *R* stereocenter and L_{rac} is a racemic lactic acid unit) were synthesized and compared with **poly LLC** (Figure 5). **Poly L*rac*LC** exhibited eight peaks in the carbonyl region. The caprolactic acid carbonyl displays a 2_2 level of sensitivity to its lactic acid nearest neighbors. The four possible sequences are LL<u>C</u>LL, L_RL<u>C</u>LL, LL<u>C</u>L_RL, and L_RL<u>C</u>L_RL. The C units on either side of the sequence isolate the central C from the influence of the next level of neighbors. The chemical shifts at δ 172.80 and δ 172.54 match well with the C carbonyl peaks of **poly LLC** (δ 172.78, LL<u>C</u>LL) and **poly L*R*LC** (δ 172.55, L_RL<u>C</u>L_RL). The other two peaks at δ 172.83 and δ 172.50 in **poly L*rac*LC** are therefore hypothesized to arise from the LL<u>C</u>L_RL and L_RL<u>C</u>LL sequences. We did not synthesize the standard, **poly LLCL*R*LC**, which would make it possible to differentiate the two signals. The four lactic acid carbonyl chemical shifts in **poly L*rac*LC** match the four lactic acid carbonyl chemical shifts found in **poly LLC** and **L*R*LC**. The four possible sequences of C<u>L</u>LC, CL<u>L</u>C, C<u>L*R*</u>LC, CL*R*<u>L</u>C are able to be assigned to the lactic acid carbonyl peaks. The caprolactic acids that surround the L units are sufficiently insulating that the next level of neighbor has no further effect on the chemical shift.

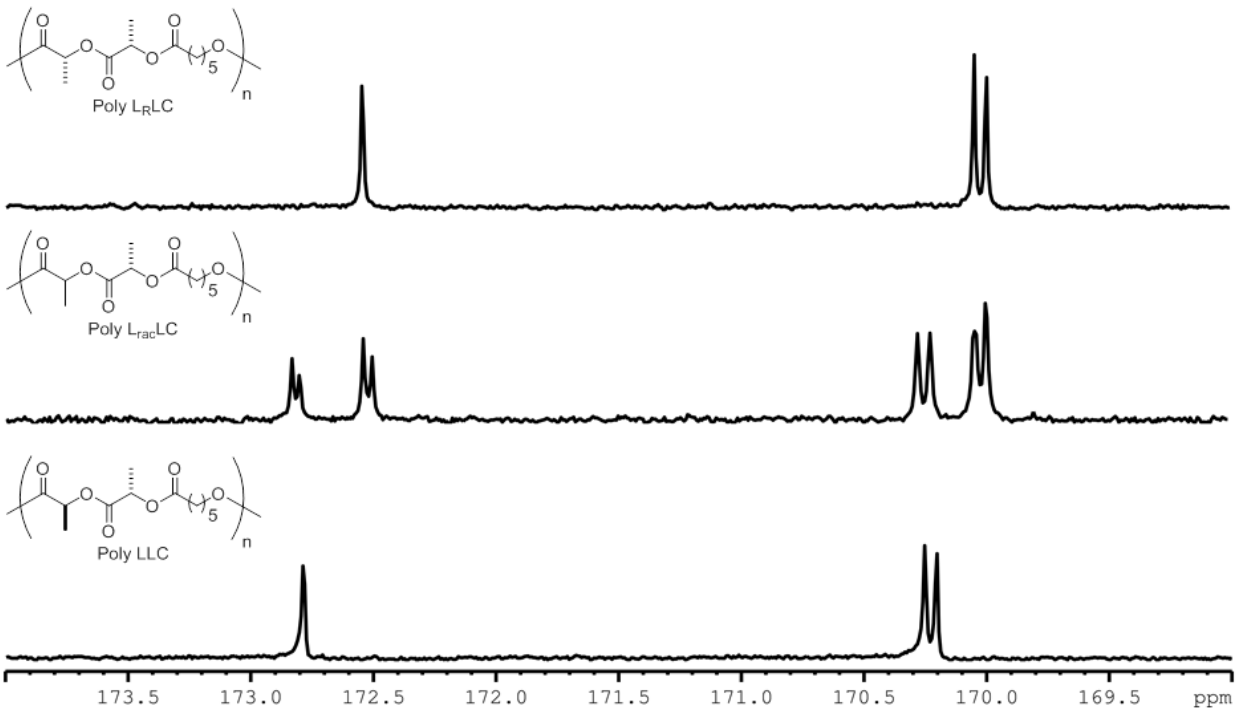


Figure 5. δ 174-169 region of the ^{13}C NMR spectra (125 MHz, $CDCl_3$) of **poly L*R*LC** (top), **poly L*rac*LC** (middle), and **poly LLC** (bottom).

By condensing segmers of known sequence of C, G, and L to form the three RSC families we are able to decipher complex ^{1}H and ^{13}C NMR spectra. Furthermore, the narrow peak widths that are inherent in repeating sequence copolymers, for example **poly LLC** (**Figure 6**), allow for detailed assignments. In the RSCs of polymers containing only L and G that we have characterized previously, the methylene of the glycolic unit proved to be very sensitive to the stereochemistry of the lactic units in the sequence, in some cases exhibiting sensitivity for the relative stereochemistries of L monomers located 4 monomer units in either direction.[15] We have found that while lactic units did create chemically inequivalent environments for nearby glycolic and caprolactic (α and ε) methylenes in the currently studied series, the increased length and flexibility of the caprolactic unit diminishes the influence of stereochemistry on the ^{1}H NMR chemical shifts. In **poly GCLC**, in which the L stereocenter is insulated by a pair of caprolactic units, for example, diastereotopicity is not observable in the glycolic acid unit—the geminal

protons exhibit the same chemical shift (**Figure 7**). When a lactic unit is located on either side of a caprolactic unit, however, the neighboring α and ε methylenes of the caprolactic monomer are diastereotopic and present as a pair of doublets of triplets. The methylene protons are split vicinally by the neighboring caprolactic internal methylenes and then split geminally by each other.

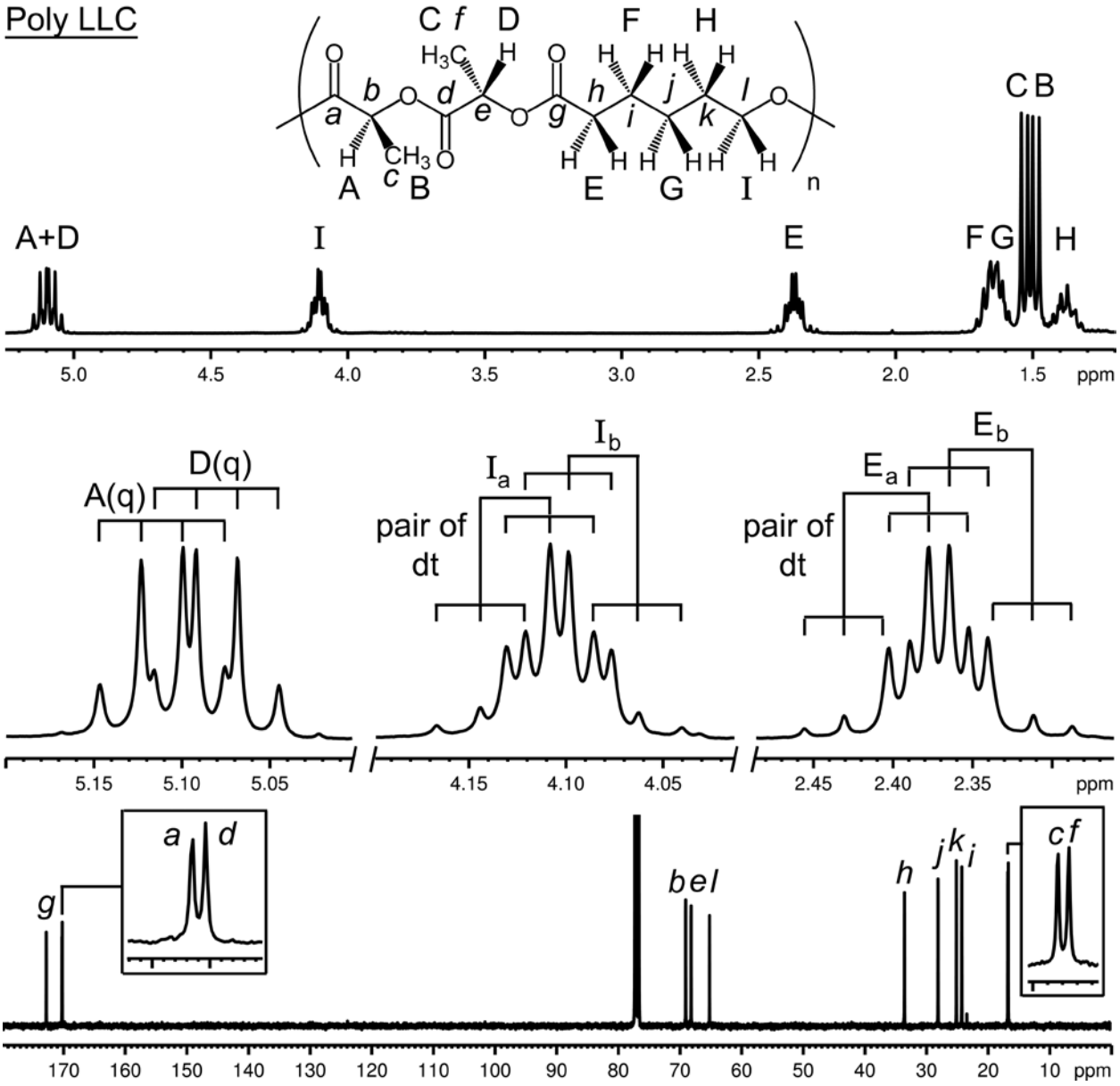


Figure 6. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 25 ºC) of (top) **poly LLC**; (middle) expansion focusing on selected multiplets; (bottom) ^{13}C NMR spectrum (75 MHz, $CDCl_3$, 25 ºC).

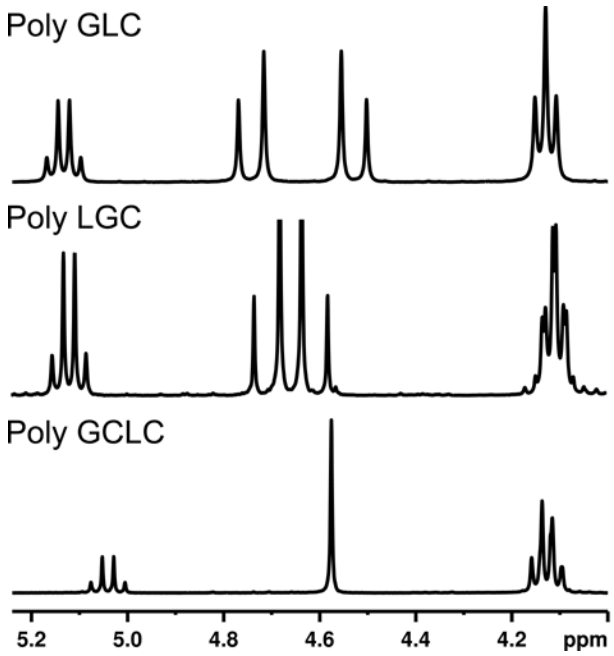


Figure 7. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 25 ºC) for RSC terpolymers **poly GLC**, **poly LGC**, and **poly GCLC**. Range: δ 5.2-4.0.

As copolyesters bearing caprolactic units have been the subject of many previous studies,[26,75,76,81] significant prior effort has been made to interpret the microstructures of the random copolymers. The general approach of preparing materials by varying comonomer ratios and then assigning NMR resonance by statistical analysis has been carried out for the various classes of copolymer: PLCA, PGCA, and PLGCA. These very thorough studies, which primarily focus on the ^{13}C NMR resonances for the carbonyl groups, have provided great insight into the structure function relationships for these classes of copolymers.[74,83-87]

We have been able using our RSC standards to verify the ^{13}C NMR assignments reported by others for PLCAs and PGCAs. A figure illustrating the correspondence is available in **Figure 8** and **Figure 9**. The greatest challenge in assembling the data for comparison was the determination of the convention for expressing sequence order employed in particular articles. In the ambiguous cases, our assignments determined from the RSCs were used to determine the convention used. Once the sequences were aligned in the same C-O direction, however, the

sequence information obtained from the RSCs of PLCA and PGCA were generally found to be consistent with the assignments based on the statistical copolymers. There were differences in exact chemical shift, particularly for the PGCAs which were analyzed in DMSO-d_6 at different temperatures, but the chemical shift regions and relative assignments corresponded.

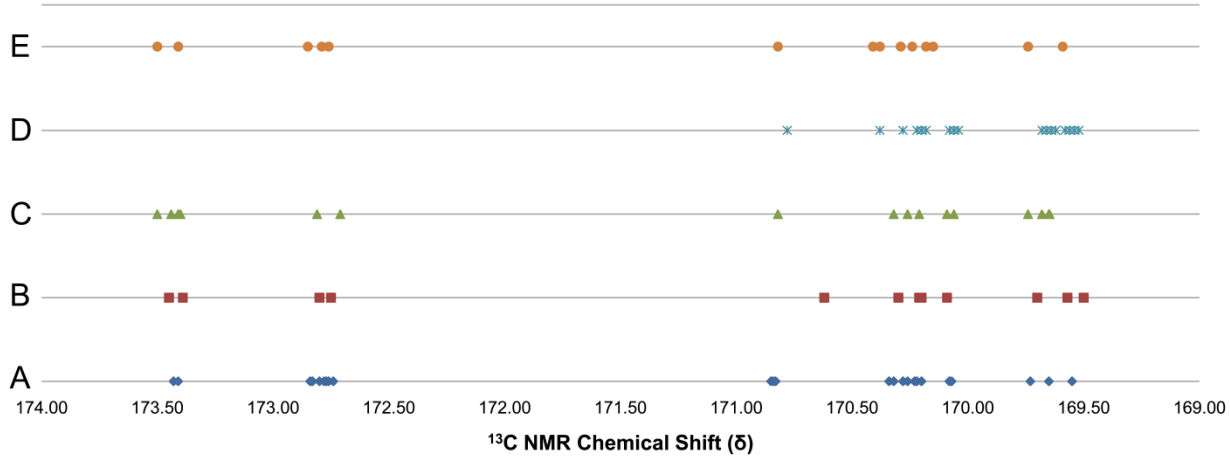


Figure 8. ^{13}C NMR chemical shifts of the caprolactic and lactic regions of RSCs of PLCA (A) and statistical PLCA chemical shifts from the literature (B[83], C[74], D[84], and E[85]).

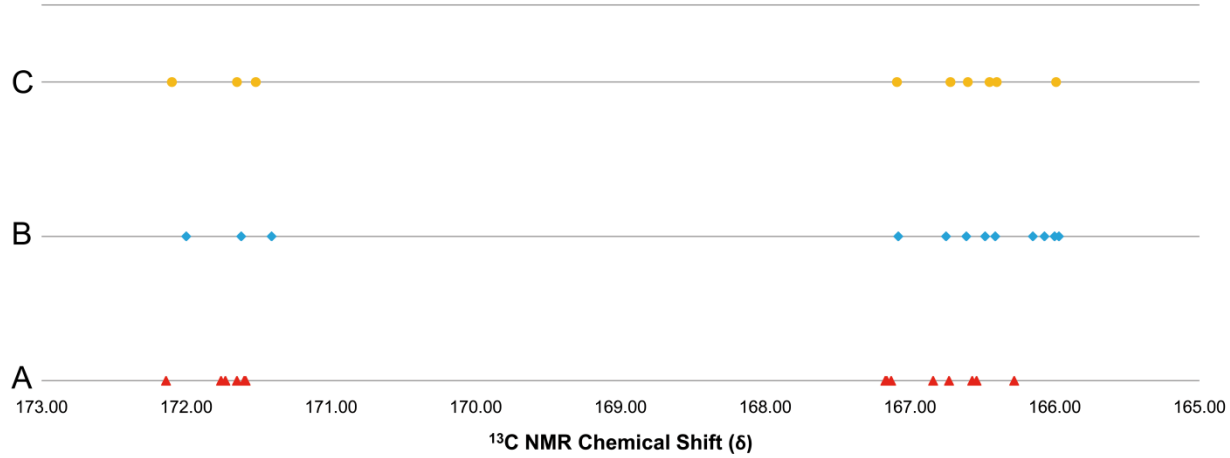


Figure 9. ^{13}C NMR chemical shifts of the caprolactic and glycolic regions of RSCs of PGCA (A) at 86 ºC in DMSO and statistical PGCA chemical shifts from the literature (B[86] and C[87]) at 100 ºC in DMSO.

2.2.4 Thermal data and analysis of sequenced copolymers containing L, G, and C

The RSCs synthesized were analyzed by DSC to investigate their thermal properties. The copolymers exhibited T_gs ranging from -49.7 to 17.9 ºC (Table 2). The introduction of caprolactic acid decreased the T_gs relative to PLGAs.[15] Although most of the polymers were amorphous, a few were semi-crystalline; T_ms ranged from 2.7 to 67.3 ºC. Polymorphism, as evidenced by multiple T_m transitions, was observed for four of the RSCs. This phenomenon is common in aliphatic polyesters.[88]

The thermal behavior of the binary RSCs, polymers containing only C and L or only C and G, depended primarily on the mole ratios of the two monomers involved rather than sequence. For example, in samples with only C and L units, it was observed as the χ_C is increased in the polymer, the T_g decreased and approached the T_g of ring opened poly(ε-caprolactone) (**Figure 10**, numerical data is compiled in the appendix in **Table 13** and **Table 14**). An analogous trend is observed for RSCs comprising only C and G units. In both systems, polymers with the same composition but different sequences exhibited nearly the same T_g.

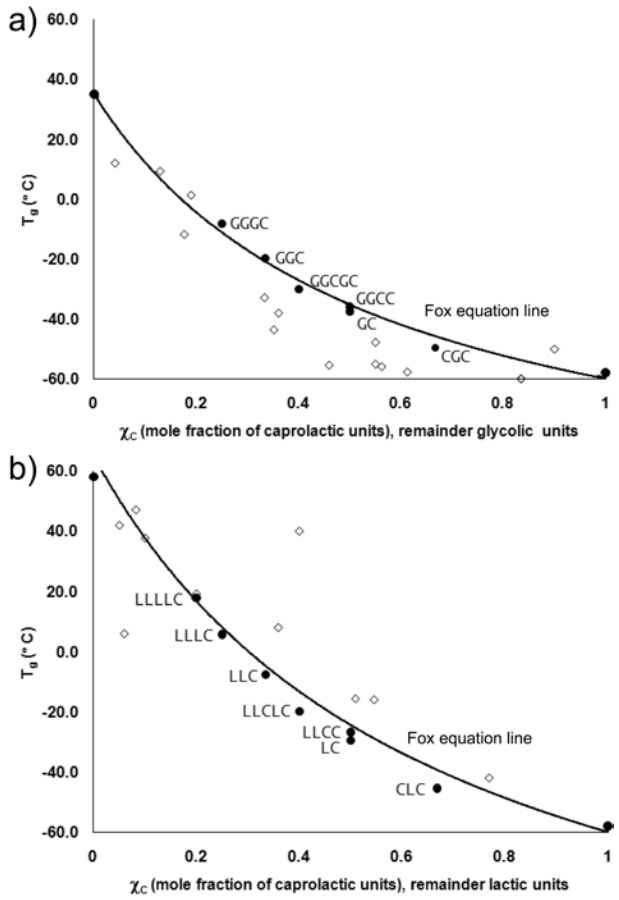


Figure 10. Comparison of χ_C (mole fraction of caprolactic units) and T_g for RSCs (filled) and random copolymers obtained by ROP (open). a) PGCA RSCs and random copolymers of C + G. b) PLCA RSCs and random copolymers of C + L. Solid line represents the Fox Equation prediction. T_gs for ROP-synthesized PGA, PLLA, PCL and their random copolymers were obtained from the literature.[26,29,89-96]

In contrast with the binary RSCs, sequence dependence of the thermal properties and morphology of the ternary PLGCA RSCs was observed. A difference of 6 ºC between the T_gs of **poly GLC** and **poly LGC** was observed despite the fact that the samples have comparable M_ns (29.4 and 27.3 kDa) and the difference increases to 8 ºC after annealing. Moreover, **poly GLC** was crystalline with a T_m of 37.7 ºC, while **poly LGC** was amorphous. **Poly GCLC** had an intermediate T_g (-34.4 ºC) between those of **poly GC** (-37.6 ºC) and **poly LC** (-29.6 ºC).

The T_gs of the RSCs of PLCA and PGCA match well to those predicted by the Fox equation while those of the random copolymers reported by others are more scattered and show a lower correspondence. The Fox equation predicts that the T_g of a binary copolymer is dependent on the

weight percent of each monomer in the copolymer and the T_g of each monomer's homopolymer (eq. 1, w_A = weight fraction monomer A).[97] The RSCs of PLCA, PGCA, and PLGCA described herein exhibited T_gs that corresponded extremely well with those predicted by the Fox equation. Random PGCAs, in contrast, showed a high degree of scattering and the T_gs were significantly lower than the predicted values from the Fox equation.[26,29,90-92] PLCAs while less scattered, exhibited T_gs higher than those expected.[26,89,91,93-96] The deviations from theory for the random copolymers are likely due to the presence of long homopolymer blocks.[98,99]

$$\frac{1}{T_g} = \frac{w_A}{T_{gA}} + \frac{w_B}{T_{gB}} \qquad (1)$$

Poly GLC and **poly LGC** are predicted to have the same T_g from the Fox equation, but **poly GLC** exhibited a higher T_g than predicted, while **poly LGC** a lower T_g than predicted. This deviation can most likely be attributed to the specific sequence of the RSC. Although we have reported only one example of sequence specific thermal behavior in our RSCs, it is expected as more complex sequences are created; more sequence dependent properties will emerge.

2.3 CONCLUSIONS

We have prepared a series of RSCs of PGCA, PLCA, and PLGCA with exact and known sequences. By creating a large set of standard polymers and exploiting the unusually well-resolved spectra that are characteristic of these RSCs, we have been able to unambiguously assign the ^1H and ^{13}C NMR spectra for these materials. This database was further used to confirm the previously reported assignments proposed by others for random copolymers. Thermal properties of the RSCs of PLCA and PGCAs were dependent on the monomer composition and correlated well with theory while thermal properties of RSCs of PLGCA exhibited exciting

sequence specific thermal behavior. Future work will focus on identifying other examples of sequence-specific behavior and on incorporating the caprolactic monomer into our group's studies of RSCs in biomaterials.

2.4 EXPERIMENTAL

Materials. ε-caprolactone (99%) was purchased from Acros and used without purification. Dicyclohexylcarbodiimide (DCC), dimethylaminopyridine (DMAP), and *tert*-butyldimethylchlorosilane (TBDMSCl) (99%) were purchased from Oakwood and used as is. Diisopropylcarbodiimide (DIC) was purchased from Anaspec and Aldrich and 4-(Dimethylamino)pyridinium 4-toluenesulfonate (DPTS) was synthesized according to previous literature.[82] THF (99.5%) was purchased from EMD and used without further purification. Ethyl acetate (Mallinckrodt) and methylene chloride (EMD) were distilled under nitrogen from calcium hydride. Column chromatography was performed using EMD 60 Å, 40-63 μm standard grade silica. Benzyl protected acids (**Bn-C**, **Bn-L**, **Bn-L$_{R}$**, **Bn-L$_{rac}$**, **Bn-G**) and silyl protected alcohols (**C-SiR$_3$** and **G-SiR$_3$**) were prepared according to previous literature.[15,59,60]

NMR Spectroscopy. ^{1}H (300 MHz, 400 MHz, 500 MHz, 600 MHz, and 700 MHz) and ^{13}C (75 MHz, 100 MHz, 125 MHz, 150 MHz, and 175 MHz) NMR spectra in $CDCl_3$ were obtained from Bruker spectrometers and calibrated to the residual solvent peaks (δ 7.24 and δ 77.0 respectively). 2D NMR experiments were recorded with Bruker 400, 500, 600 and 700 MHz NMR spectrometers equipped with a 5 mm gradient probe using HMBC and HMQC gradient pulse sequences. High temperature ^{13}C NMR spectra for RSCs of PGCA were obtained in DMSO-d_6 at 86.1 ºC (temperature internally calibrated using 80% ethylene glycol in DMSO).

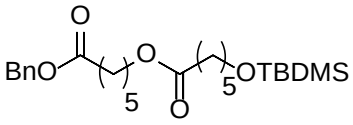
Molecular Weight Analysis. HRMS data were acquired on a Waters LC/Q-TOF instrument. Elemental analysis was performed independently by Atlantic Microlab, Inc., Norcross, GA. Molecular weights and polydispersities were acquired on a Waters GPC (THF) with Jordi 500 Å, 1000 Å and 10000 Å divinylbenzene (DVB) columns and refractive index detector (Waters) was calibrated to polystyrene standards.

Thermal Analysis. Differential Scanning Calorimetry (DSC) experiments were performed with a TA Instruments Q200 DSC. Standard data were collected with a heating a cooling rate of 10 ºC/min and T_ms were collected from the first heating cycle, while T_gs were collected in the second heating cycle. Annealed samples were prepared by drop-casting (CH_2Cl_2) into DSC pans and then drying under vacuum for 24 hours. The data for annealed samples were collected in the first heating cycle.

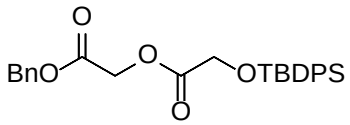
2.4.1 General procedure for DCC/DPTS coupling reactions

The TBDMS-alcohol (1-1.2 equiv.), benzyl protected-acid (1-1.2 equiv.), DPTS (0.2 equiv.), and dicyclohexylcarbodiimide (DCC, 1.1-1.5 equiv.) were combined in dry CH_2Cl_2 (0.1 M in substrate). The reaction mixture was allowed to stir overnight under N_2. Dicyclohexylurea (DCU) was removed by filtration and the resulting filtrate was concentrated *in vacuo*. The concentrate was purified by chromatography over silica using 2.5% ethyl acetate in hexanes as the eluent.

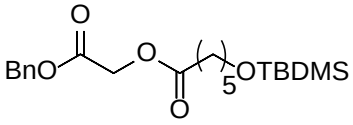
Dimers. The diprotected dimers were prepared by combining the benzyl protected acids (**Bn-C**, **Bn-G** and **Bn-L**) with **C-SiR$_3$** or **G-SiR$_3$** using the general coupling procedure.[15,59,60]



Bn-CC-SiR3. The product was a colorless liquid (15.6 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.10 (s, 2H), 4.02 (t, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.4 Hz), 2.35 (t, 2H, *J* = 7.6 Hz), 2.27 (t, 2H *J* = 7.4 Hz), 1.70-1.57 (m, 6H), 1.54-1.47 (m, 2H), 1.40-1.29 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.79, 173.31, 136.02, 128.55, 128.20, 128.18, 66.15, 64.02, 62.96, 34.32, 34.12, 32.46, 28.32, 25.95, 25.51, 25.43, 24.80, 24.55, 18.34, -5.30; HRMS (M+Na) calc mass 473.2699, found 473.2711; Anal. calcd for $C_{25}H_{42}O_5Si$: C, 66.62; H, 9.39. Found: C, 66.89; H, 9.44.

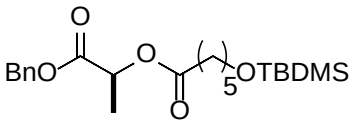


Bn-GG-SiR3. The product was a colorless liquid (10.9 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.44-7.30 (m, 11H), 5.17 (s, 2H), 4.65 (s, 2H), 4.34 (s, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ170.62, 167.30, 135.53, 134.76, 132.60, 129.90, 128.61, 128.52, 128.35, 127.80, 67.10, 61.86, 60.66, 26.60, 19.23; HRMS (M+Na) calc mass 485.1760, found 485.1741.



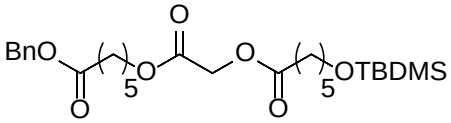
Bn-GC-SiR3. The product was a colorless liquid (20.0 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.3 (m, 5H), 5.17 (s, 2H), 4.63 (s, 2H), 3.58 (t, 2H, *J* = 6.5 Hz), 2.40 (t, 2H, *J* = 7.5 Hz), 1.7-1.6 (m, 2H), 1.6-.4 (m, 2H), 1.4-1.2 (m, 2H), 0.87 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 173.01, 167.77, 135.05, 128.61, 128.37, 67.03, 62.90, 60.52, 33.76, 32.40, 25.94, 25.30, 24.60, 18.32, -5.31; HRMS (M+Na) calc mass 417.2073, found 417. 2108.

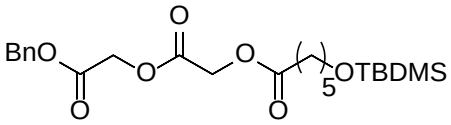


Bn-LC-SiR$_3$. The product was a colorless liquid (9.64 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.12 (q, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.36 (dt, J_1 = 15.6 Hz, J_2 = 7.8 Hz, 1H), 2.35 (t, J_1 = 15.6 Hz, J_2 = 7.4 Hz, 1H), 1.63 (m, 2H), 1.51 (m, 2H), 1.47 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.04, 170.72, 135.35, 128.56, 128.35, 128.10, 68.38, 66.91, 62.92, 33.94, 32.42, 25.94, 25.33, 24.61, 18.32, 16.89, -5.31; HRMS (M+Na) calc mass 431.2230, found 431.2240.

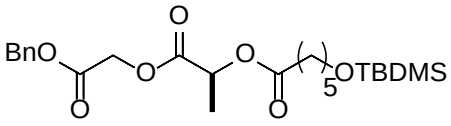
Trimers. The diprotected trimers were prepared by combining the benzyl protected acids (**Bn-C**, **Bn-G**, and **Bn-L**) with the silyl protected alcohol dimers (**GC-SiR$_3$**, **CC-SiR$_3$** and **LC-SiR$_3$**) using the general coupling procedure.



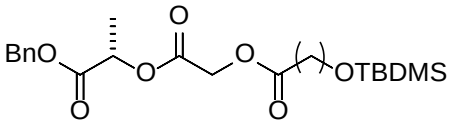
Bn-CGC-SiR$_3$. The product was a colorless liquid (11.10 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.09 (s, 2H), 4.56 (s, 2H), 4.12 (t, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.40 (t, 2H, *J* = 7.7 Hz), 2.35 (t, 2H, *J* = 7.5 Hz), 1.71-1.60 (m, 6H), 1.66-1.56 (m, 2 H), 1.43-1.38 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.25, 173.02, 167.93, 135.97, 128.54, 128.20, 66.16, 65.08, 62.91, 60.50, 34.05, 33.77, 32.41, 28.15, 25.94, 25.32, 24.61, 24.45, 18.33, -5.31; HRMS (M+Na) calc mass 531.2754, found 531.2711.



Bn-GGC-SiR3. The product was a colorless liquid (6.85 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.18 (s, 2H), 4.71 (s, 2H), 4.70 (s, 2H), 3.58 (t, 2H, *J* = 6.3 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 1.72-1.62 (m, 2H), 1.56-1.45 (m, 2H), 1.41-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.91, 167.40, 166.97, 134.87, 128.66, 128.62, 128.44, 67.29, 62.92, 61.04, 60.16, 33.71, 32.41, 25.95, 25.31, 24.58, 18.34, -5.30; HRMS (M+Na) calc mass 475.2128, found 475.2148.

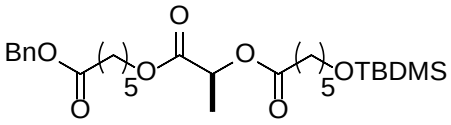


Bn-GLC-SiR3. The product was a colorless liquid (6.04 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.17 (s, 2H), 5.13 (q, 1H, *J* = 7.2 Hz), 4.80 (d, 1H, *J* = 15.9 Hz), 6.89 (d, 1H, *J* = 15.9 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 1.70-1.60 (m, 2H), 1.53-1.44 (m, 2H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.40-1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173. 03, 170.35, 167.06, 134.89, 128.63, 128.46, 68.12, 67.23, 62.94, 60.94, 33.86, 32.42, 31.57, 25.94, 25.33, 24.57, 22.64, 18.33, 16.84, 14.11, -5.31; HRMS (M+Na) calc mass 489.2285, found 489.2265.

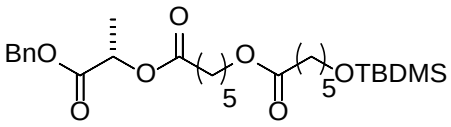


Bn-LGC-SiR3. The product was a colorless liquid (10.40 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.20 (q, 1H, *J* = 7.2 Hz), 5.18 (d, 1H, *J* = 12.3 Hz), 5.14 (d, 1H, *J* = 12.3 Hz), 4.72 (d, 1H, *J* = 16.2 Hz), 4.62 (d, 1H, *J* = 16.2 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.40 (t, 2H, *J*

= 7.7 Hz), 1.71-1.61 (m, 2H), 1.54-1.47 (m, 2H), 1.50 (d, 3H, *J* = 7.2 Hz), 1,43-1.31 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.91, 169.93, 167.33, 135.13, 128.16, 128.45, 128.15, 69.27, 67.17, 62.91, 60.26, 33.72, 32.41, 25.94, 25.31, 24.59, 18.33, 16.83, -5.31; HRMS (M+Na) calc mass 489.2285, found 489.2246.

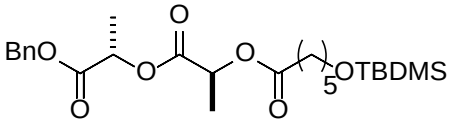


Bn-CLC-SiR$_3$. The product was a colorless liquid (8.14 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.09 (s, 2H), 5.03 (q, 1H, *J* = 7.2 Hz), 4.10 (t, 2H, *J* = 6.8 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 2.35 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.34 (t, 2H, *J* = 7.4 Hz), 1.70-1.58 (m, 6H), 1.56-1.46 (m, 2H), 1.44 (d, 3H, *J* = 7.2 Hz), 1.40-1.30 (m, 4H), 0.86 (s, 9H), 0.016 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.24, 173.04, 170.90, 135.97, 128.53, 128.19, 128.18, 68.38, 66.14, 64.99, 62.93, 34.05, 33.92, 32.42, 28.16, 25.93, 25.33, 25.30, 24.60, 24.45, 18.31, 16.94, -5.32; HRMS (M+Na) calc mass 545.2911, found 545.2905.

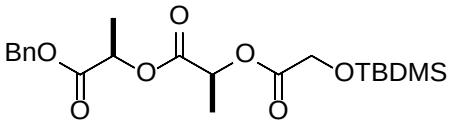


Bn-LCC-SiR$_3$. The product was a colorless liquid (6.87 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 5.18 (d, 1H, *J* = 12.4 Hz), 5.12 (d, 1H, *J* = 12.4 Hz), 5.11 (q, 1H, *J* = 7.2 Hz), 4.02 (t, 2H, *J* = 6.8 Hz), 3.58 (t, 2H, *J* = 6.4 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.28 (t, 2H, *J* = 7.6 Hz), 1.68-1.57 (m, 6H), 1.54-1.47 (m, 2H), 1.47 (d, 3H, *J* = 7.2 Hz), 1.41-1.30 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.79, 172.84, 170.69, 135.31, 128.58, 128.39, 128.12, 68.45, 66.96, 64.02, 62.96, 34.32, 33.76, 32.46, 28.29, 25.95, 25.44, 25.41, 24.80, 24.41, 18.33, 16.89, -5.30; HRMS (M+K)

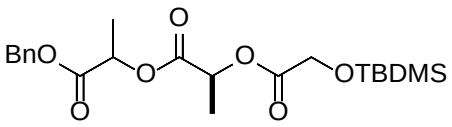
calc mass 561.2650; found 561.2622; Anal. calcd for $C_{28}H_{46}O_7Si$: C, 64.33; H, 8.87. Found: C, 64.45; H, 9.07.



Bn-LLC-SiR$_3$. The product was a colorless liquid (5.36 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.18 (q, 1H, *J* = 7.2 Hz), 5.17 (d, 1H, *J* = 12.3 Hz), 5.11 (d, 1H, *J* = 12.0 Hz), 5.07 (q, 1H, *J* = 7 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 1.69-1.59 (m, 2H), 1.55-1.46 (m, 2H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 7.2 Hz), 1.40-1.30 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.12, 170.33, 170.09, 135.10, 128.59, 128.46, 128.22, 69.03, 68.12, 67.13, 62.93, 33.85, 32.42, 25.94, 25.31, 24.57, 18.32, 16.78, 16.69, -5.31; HRMS (M+Na) calc mass 503.2441, found 503.2395.

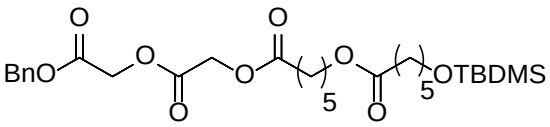


Bn-L$_R$LC-SiR$_3$. The product was a colorless liquid (3.28 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.19 (d, 1H, *J* = 12.4 Hz), 5.16 (q, 1H, *J* = 7.1 Hz), 5.13 (d, 1H, *J* = 12.4 Hz), 5.13 (q, 1H, *J* = 7.1 Hz), 3.58 (t, 2H, *J* = 6.4 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.6 Hz), 2.35 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 1.68-1.61 (m, 2H), 1.54-1.46 (m, 2H), 1.48 (d, 3H, *J* = 6.8 Hz), 1.47 (d, 3H, *J* = 7.2 Hz), 1.40-1.32 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.86, 170.14, 169.87, 135.20, 128.57, 128.42, 128.22, 69.16, 68.32, 67.11 62.93, 33.91, 32.43, 25.95, 25.36, 24.64, 18.33, 16.86, 16.80, -5.30; HRMS (M+Na) calc mass 503.2441, found 503.2416.

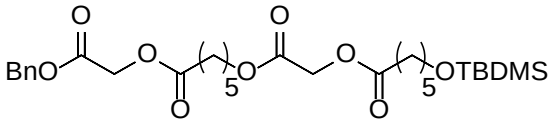


Bn-L*rac*LC-SiR3. The product was a colorless liquid (4.74 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 10H), 5.21-5.10 (m, 7H), 5.07 (q, 1H, *J* = 7.1 Hz), 3.58 (t, 4H, *J* = 6.4 Hz), 2.43-2.32 (m, 4H), 1.66-1.62 (m, 4H), 1.52-1.46 (m, 16H), 1.39-1.34 (m, 4H), 0.87 (s, 18H), 0.02 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.12, 172.86, 170.33, 170.14, 170.09, 169.87, 135.19, 135.13, 128.60, 128.57, 128.47, 128.42, 128.22, 69.16, 69.04, 68.32, 68.13, 67.13, 67.11, 62.95, 62.93, 33.91, 33.87, 32.43, 25.95, 25.36, 25.33, 24.63, 24.59, 18.33, 16.86, 16.79, 16.70, -5.30; HRMS (M+Na) calc mass 503.2441, found 503.2469.

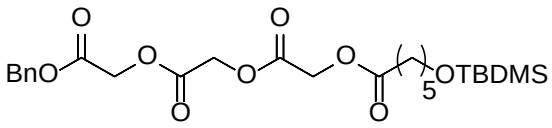
Tetramers. The diprotected tetramers were prepared by combining the benzyl protected acid dimers (**Bn-GC**, **Bn-GG**, **Bn-LC**, and **Bn-LL**) with the silyl protected alcohol dimers (**GC-SiR3**, **CC-SiR3** and **LC-SiR3**) using the general coupling procedure unless otherwise notated.



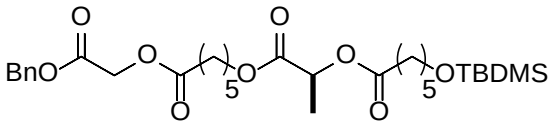
Bn-GGCC-SiR3. The product was a colorless liquid (6.94 g, quantitative). ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.38-7.30 (m, 5H), 5.18 (s, 2H), 4.71 (s, 4H), 4.04 (t, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.6 Hz), 2.42 (t, 2H, *J* = 7.4 Hz), 2.28 (t, 2H, *J* = 7.6 Hz), 1.72-1.57 (m, 6H), 1.54-1.47 (m, 2H), 1.43-1.29 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 172.68, 167.35, 166.94, 134.87, 128.66, 128.62, 128.43, 67.30, 64.00, 62.96, 61.05, 60.19, 34.31, 33.54, 32.46, 28.29, 25.95, 25.43, 25.39, 24.79, 24.37, 18.33, -5.30; HRMS (M+Na) calc mass 589.2809, found 589.2840.



Bn-GCGC-SiR3. The product was a colorless liquid (9.10 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 5.17 (s, 2H), 4.63 (s, 2H), 4.57 (s, 2H), 4.13 (t, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 2.40 (t, 2H, *J* = 7.5 Hz), 1.71-1.59 (m, 6H), 1.56-1.47 (m, 2H), 1.44-1.31 (m, 4H), 0.86 (s, 9H), 0.017 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.01, 172.74, 167.93, 167.72, 135.02, 128.62, 128.54, 128.38, 67.07, 65.05, 62.91, 60.57, 60.51, 33.77, 33.54, 32.41, 28.12, 25.94, 25.32, 25.19, 24.61, 24.33, 18.32, 14.18, -5.31; HRMS (M+Na) calc mass 589.2809, found 589.2761.

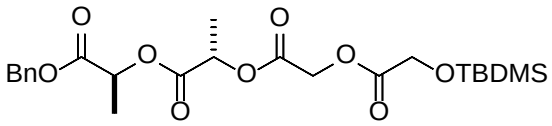


Bn-GGGC-SiR3. The product was a colorless liquid (2.86 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 5H), 5.18 (s, 2H), 4.79 (m, 2H), 4.72 (s, 2H), 4.71 (s, 2H), 3.58 (t, 2H, *J* = 6.4 Hz), 2.41 (t, 2H, *J* = 7.4 Hz), 1.70-1.63 (m, 2H), 1.55-1.48 (m, 2H), 1.41-1.33 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.90, 167.30, 166.81, 166.59, 134.82, 128.67, 128.65, 128.45, 67.35, 62.91, 61.17, 60.66, 60.11, 33.70, 32.40, 25.94, 25.31, 24.56, 18.33, -5.31; HRMS (M+Na) calc mass 533.2183, found 533.2200.

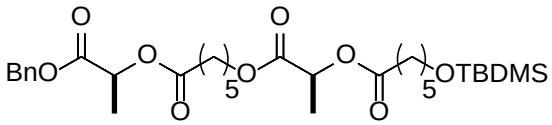


Bn-GCLC-SiR3. The product was a colorless liquid (5.01 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.31 (m, 5H), 5.17 (s, 2H), 5.04 (q, *J* = 7.0 Hz, 1H) 4.63 (s, 2H), 4.10 (m, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.40 (t, 2H, *J* = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.7 Hz), 2.36

(dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 1.71-1.58 (m, 6H), 1.56-1.43 (m, 2H), 1.45 (d, 3H, J = 7.0 Hz), 1.41-1.30 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.05, 172.74, 170.91, 167.72, 135.02, 128.62, 128.54, 128.38, 68.39, 67.07, 64.98, 62.94, 60.57, 33.93, 33.55, 32.43, 28.14, 25.94, 25.34, 25.19, 24.62, 24.33, 18.33, 16.96, -5.31; HRMS (M+Na) calc mass 603.2965, found 603.2957.

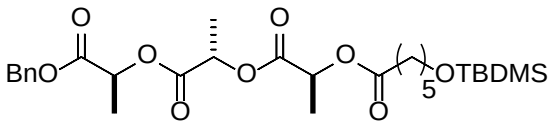


Bn-LLCC-SiR$_3$. The product was a colorless liquid (4.57 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.18 (q, 1H, J = 7.2 Hz), 5.17 (d, 1H, J = 12.0 Hz), 5.12 (d, 1H, J = 12.4 Hz), 5.07 (q, 1H, J = 7.2 Hz), 4.03 (t, 2H, J = 6.6 Hz), 3.58 (t, 2H, J = 6.6 Hz), 2.38 (dt, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.0 Hz), 2.27 (t, 2H, J = 7.6 Hz), 1.69-1.57 (m, 6H), 1.54-1.47 (m, 2H), 1.51 (d, 3H, J = 7.2 Hz), 1.47 (d, 3H, J = 7.2 Hz), 1.42-1.30 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 172.90, 170.30, 170.07, 135.11, 128.60, 128.48, 128.23, 69.06, 68.20, 67.14, 64.02, 62.96, 34.32, 33.68, 32.46, 28.30, 25.95, 25.43, 25.40, 24.79, 24.38, 18.34, 16.79, 16.69, -5.30; HRMS (M+Na) calc mass 617.3122, found 617.3118.



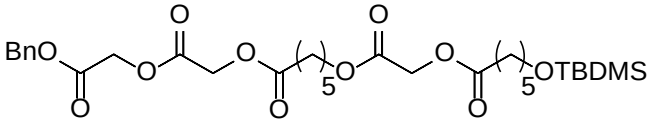
Bn-LCLC-SiR$_3$. The product was a colorless liquid (8.17 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 5.18 (d, 1H, J = 12.3 Hz), 5.12 (d, 1H, J = 12.3 Hz), 5.10 (q, 1H, J = 7.2 Hz), 5.04 (q, 1H, J = 7.2 Hz), 4.15-4.03 (m (pair of dt), 2H), 3.58 (t, 2H, J = 6.3 Hz), 2.45-2.28 (m (two pairs of dt), 4H), 1.70-1.57 (m, 6H), 1.56-1.44 (m, 2H), 1.47 (d, 3H, J = 7.2 Hz), 1.45 (d, 3H, J = 7.2 Hz), 1.41-1.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.04, 172.78, 170.09,

170.67, 135.28, 128.57, 128.38, 128.12, 68.45, 68.38, 66.95, 65.00, 62.93, 33.92, 33.70, 32.42, 28.14, 25.33, 25.20, 24.61, 24.32, 18.32, 16.95, 16.87, -5.31; HRMS (M+Na) calc mass 617.3146, found 617.3148.



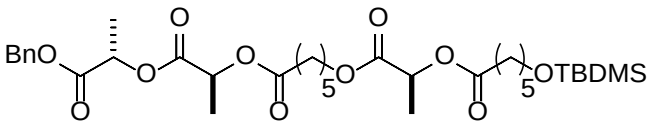
Bn-LLLC-SiR$_3$. The product was a clear yellow liquid (27.3 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.20-5.04 (m, 5H), 3.57 (t, 2H, J = 6.5 Hz), 2.38 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 2.36 (t, 1H, J_1 = 15.9 Hz, J_2 = 7.2 Hz), 1.69-1.59 (m, 2H), 1.55-1.46 (m, 2H), 1.53 (d, 3H, J = 6.9 Hz), 1.51 (d, 3H, J = 6.9 Hz), 1.50 (d, 3H, J = 7.2 Hz), 1.40-1.30 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.14, 170.39, 169.95, 169.72, 135.06, 128.60, 128.50, 128.24, 69.18, 68.81, 68.10, 67.18, 62.94, 33.86, 32.43, 25.94, 25.32, 24.58, 18.33, 16.75 (2), 16.57, -5.31; HRMS (M+Na) calc mass 575.2652, found 575.2595.

Pentamers. The diprotected pentamers were prepared by combining the benzyl protected acids (**Bn-G** and **Bn-L**) with the silyl protected alcohol tetramers (**GCGC-SiR$_3$**, **LCLC-SiR$_3$**, and **LLLC-SiR$_3$**) using the general coupling procedure.

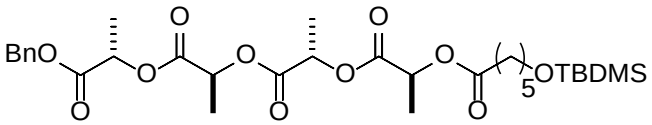


Bn-GGCGC-SiR$_3$. The product was a colorless liquid (6.03 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 5.18 (s, 2H), 4.71 (s, 2H), 4.63 (s, 2H), 4.14 (t, 2H, J = 6.6 Hz), 3.58 (t, 2H, J = 6.5 Hz), 2.42 (t, 2H, J = 7.5 Hz), 2.40 (t, 2H, J = 7.5 Hz), 1.73-1.60 (m, 6H), 1.56-1.47 (m, 2H), 1.45-1.31 (m, 4H), 0.86 (s, 9H), 0.018 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.02, 172.62, 167.94, 167.34, 166.94, 134.86, 128.65, 128.62, 128.43, 67.29, 65.05, 62.92,

61.04, 60.51, 60.19, 33.77, 33.48, 32.42, 28.13, 25.94, 25.32, 25.19, 24.61, 24.29, 18.33, -5.31; HRMS (M+Na) calc mass 647.2864, found 647.2803.



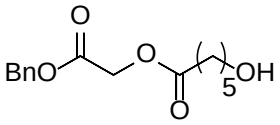
Bn-LLCLC-SiR$_3$. The product was a colorless liquid (4.42 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 5H), 5.18 (q, 1H, *J* = 7.2 Hz), 5.17 (d, 1H, *J* = 12.6 Hz), 5.11 (d, 1H, *J* = 12.0 Hz), 5.07 (q, 1H, *J* = 7.2 Hz), 5.03 (q, 1H, *J* = 7.2 Hz), 4.10 (m (pair of dt), 2H), 3.58 (t, 2H, *J* = 6.5 Hz), 2.45-2.28 (m (2 pairs of dt), 4H), 1.70-1.59 (m, 6H), 1.56-1.42 (m, 2H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 7.2 Hz), 1.45 (d, 3H, *J* = 7.2 Hz), 1.41-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.05, 172.85, 170.91, 170.29, 170.06, 135.07, 128.59, 128.47, 128.22, 69.05, 68.38, 68.20, 67.14, 65.01, 62.94, 33.93, 33.62, 32.43, 28.15, 25.94, 25.34, 25.20, 24.61, 24.30, 18.33, 16.95, 16.78, 16.68, -5.31; HRMS (M+) calc mass 666.343542, found 666.343059.



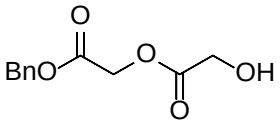
Bn-LLLLC-SiR$_3$. The product was a colorless liquid (5.48 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 5.20-5.05 (m, 6H), 3.58 (t, 2H, *J* = 6.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.7 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz), 1.69-1.59 (m, 2H), 1.58-1.46 (m, 2H), 1.57 (d, 3H, *J* = 6.9 Hz), 1.53 (d, 3H, *J* = 7.2 Hz), 1.50 (d, 3H, *J* = 7.2 Hz), 1.50 (d, 3H, *J* = 7.2 Hz), 1.43-1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.14, 170.41, 169.92, 169.78, 169.58, 135.04, 128.61, 128.51, 128.25, 69.24, 68.92, 68.80, 68.09, 67.20, 62.94, 33.86, 32.43, 25.95, 25.32, 24.58, 18.33, 16.75, 16.64, 16.56, -5.30; HRMS (M+Na) calc mass 647.2864, found 647.2830.

2.4.2 General procedure for the silyl deprotections.

The diprotected oligomers were combined with 1.5 equiv. tetrabutylammonium fluoride (TBAF), and 8.0 equiv. glacial acetic acid (AcOH) in THF (0.1 M in substrate) and stirred overnight at RT, unless otherwise noted. The reaction mixture was added to 300 mL of brine and 250 mL of Et_2O and the layers were separated. The aqueous layer was washed with Et_2O (2 × 200 mL) and the organic layers were combined, dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was purified by chromatography over silica using 5-15% EtOAc in hexanes as the eluent.[15]

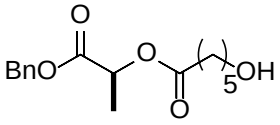


Bn-GC. The product was a clear yellow liquid (5.72 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.17 (s, 2H), 4.63 (s, 2H), 3.61 (t, 2H, *J* = 6.5 Hz), 2.41 (t, 2H, *J* = 7.4 Hz), 1.72-1.62 (m, 2H), 1.61-1.51 (m, 3H), 1.46-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 167.82, 134.98, 128.60, 128.52, 128.36, 67.08, 62.49, 60.53, 33.66, 32.18, 25.03, 24.44; HRMS (M+Na) calc mass 303.1208, found 303.1212.

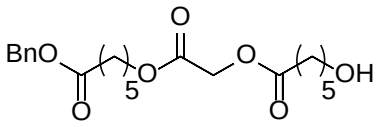


Bn-GG. The reaction was carried out according to the general procedure for silyl deprotection except the reaction was stirred for 1 h at RT. The product was a white solid (3.33 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 5.19 (s, 2H), 4.74 (s, 2H), 4.28 (d, 2H, *J* = 5.6 Hz), 2.52 (t, 1H, *J* = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68, 167.12, 134.79, 128.66,

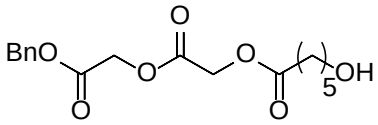
128.41, 67.34, 61.09, 60.42; HRMS (M+Na) calc mass 224.068474, found 224.068223; Anal. calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.11; H, 5.30.



Bn-LC. The product was a colorless liquid (4.94 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.18 (d, 1H, *J* = 12.3 Hz), 5.12 (d, 1H, *J* = 12.6 Hz), 5.11 (q, 1H, *J* = 7.2 Hz), 3.61 (t, 2H, *J* = 6.3 Hz), 2.38 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.2 Hz), 1.70-1.60 (m, 2H), 1.57-1.50 (m, 2H), 1.47 (d, 3H, *J* = 7.2 Hz), 1.44-1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.02, 170.78, 135.25, 128.56, 128.37, 128.10, 68.41, 66.96, 62.52, 33.81, 32.19, 25.02, 24.42, 16.87; HRMS (M+Na) calc mass 317.1365, found 317.1342.

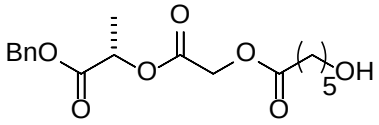


Bn-CGC. The product was a yellow clear liquid (6.82 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.09 (s, 2H), 4.57 (s, 2H), 4.12 (t, 1H, *J* = 6.6 Hz), 3.65-3.60 (m, 2H), 2.42 (t, 2H, *J* = 7.4 Hz), 2.35 (t, 2H, *J* = 7.4 Hz), 1.74-1.53 (m, 8H), 1.47-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.29, 172.97, 167.98, 135.96, 128.55, 128.22, 128.20, 66.18, 65.15, 62.52, 60.53, 34.05, 33.69, 32.21, 28.14, 25.32, 25.05, 24.47; HRMS (M+Na) calc mass 417.1889, found 417.1917.

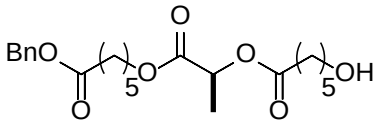


Bn-GGC. The product was a colorless liquid (6.05 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 5.13 (s, 2H), 4.67 (s, 2H), 4.66 (s, 2H), 3.55 (t, 2H, *J* = 6.5 Hz), 2.40-2.36 (m, 3H),

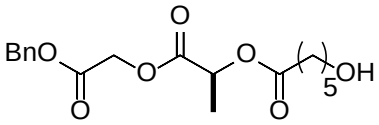
1.69-1.59 (m, 2H), 1.56-1.47 (m, 2H), 1.41-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.70, 167.26, 166.82, 134.66, 128.40, 128.36, 128.17, 67.01, 62.04, 60.82, 59.94, 33.36, 31.93, 24.87, 24.23; HRMS (M+Na) calc mass 361.1263, found 361.1229.



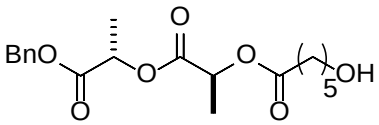
Bn-LGC. The product was a colorless liquid (3.60 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.20 (q, 1H, *J* = 7.2 Hz), 5.18 (d, 1H, *J* = 12.3 Hz), 5.14 (d, 1H, *J* = 12.3 Hz), 4.72 (d, 1H, *J* = 16.2), 4.62 (d, 1H, *J* = 16.3 Hz), 3.62 (t, 2H, *J* = 6.5 Hz), 2.42 (t, 2H, *J* = 7.4 Hz), 1.73-1.63 (m, 2H), 1.62-1.52 (m, 2H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.46-1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.86, 169.92, 167.37, 135.10, 128.45, 128.15, 69.30, 67.19, 62.54, 60.27, 33.62, 32.21, 25.06, 24.44, 16.82; HRMS (M+Na) calc mass 375.1420, found 375.1399.



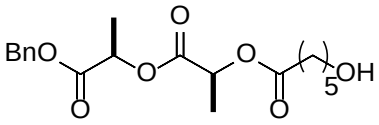
Bn-CLC. The product was a colorless liquid (2.07 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.09 (s, 2H), 5.03 (q, 1H, *J* = 7.1 Hz), 4.10 (t, 2H, *J* = 6.6 Hz), 3.65-3.59 (m, 2H), 2.39 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.39-2.29 (m (dt), 1H), 2.35 (t, 2H, *J* = 7.4 Hz), 1.72-1.52 (m, 8H), 1.45 (d, 3H, *J* = 7.1 Hz), 1.42-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.30, 173.00, 170.96, 135.96, 128.54, 128.22, 128.20, 68.43, 66.18, 65.18, 65.07, 62.52, 34.06, 33.83, 32.22, 28.16, 25.31, 25.05, 24.45, 16.94; HRMS (M+Na) calc mass 431.2046, found 431.2063.



Bn-GLC. The product was a colorless liquid (2.21 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.17 (s, 2H), 5.14 (q, 1H, *J* = 7.2 Hz), 4.80 (d, 1H, *J* = 15.9 Hz), 4.58 (d, 1H, *J* = 15.9 Hz), 3.62 (t, 2H, *J* = 6.5 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz), 2.38 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 1.72-1.62 (m, 2H), 1.61-1.52 (m, 2H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.45-1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 170.36, 167.03, 134.84, 128.61, 128.58, 128.44, 68.13, 67.22, 62.54, 60.94, 33.73, 32.20, 25.03, 24.40, 16.81; HRMS (M+Na) calc mass 375.1420, found 375.1397.

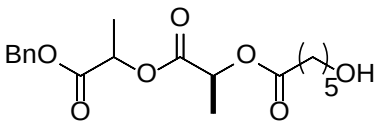


Bn-LLC. The product was a colorless liquid (3.60 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.18 (q, 1H, *J* = 7.2 Hz), 5.17 (d, 1H, *J* = 12.0 Hz), 5.11 (d, 1H, *J* = 12.3 Hz), 5.07 (q, 1H, *J* = 7.2 Hz), 3.62 (t, 2H, *J* = 6.3 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.2 Hz), 1.71-1.61 (m, 2H), 1.58-1.34 (m, 4H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.07, 170.37, 170.06, 135.09, 128.59, 128.47, 128.22, 69.07, 68.17, 67.14, 62.54, 33.74, 32.22, 25.04, 24.41, 16.77, 16.68; HRMS (M+Na) calc mass 389.1576, found 389.1583.

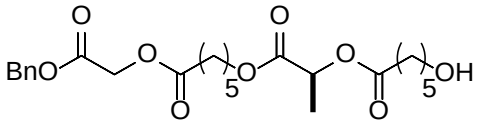


Bn-L*R*LC. The product was a colorless liquid (2.24 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.18 (d, 1H, *J* = 12.4 Hz), 5.16 (q, 1H, *J* = 7.1 Hz), 5.14 (q, 1H, J = 7.2 Hz),

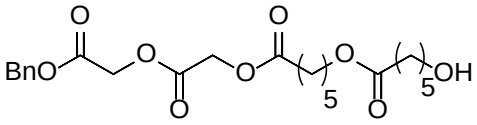
5.13 (d, 1H, J = 12.4 Hz), 3.63-3.60 (m, 2H), 2.38 (dt, 1H, J_1 = 16.0 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.70-1.63 (m, 2H), 1.59-1.51 (m, 2H), 1.48 (d, 3H, J = 6.8 Hz), 1.47 (d, 3H, J = 7.2 Hz), 1.44-1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.78, 170.14, 169.85, 135.16, 128.56, 128.40, 128.20, 69.19, 68.31, 67.12, 62.54, 33.79, 32.23, 25.11, 24.46, 16.83, 16.78; HRMS (M+Na) calc mass 389.1576, found 389.1540.



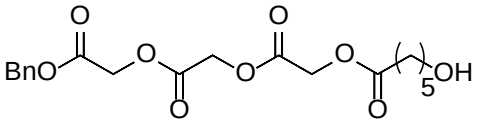
Bn-L*rac*LC. The product was a colorless liquid (3.16 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 10H), 5.21-5.11 (m, 7H), 5.07 (q, 1H, J = 7.1 Hz), 3.62 (t, 4H, J = 6.6 Hz), 2.45-2.31 (m, 4H), 1.70-1.62 (m, 4H), 1.60-1.53 (m, 4H), 1.50-1.46 (m, 12H), 1.44-1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.06, 172.78, 170.37, 170.15, 170.06, 169.85, 135.17, 135.09, 128.59, 128.56, 128.46, 128.41, 128.21, 69.20, 69.07, 68.32, 68.17, 67.14, 67.12, 62.55, 33.80, 33.75, 32.23, 25.11, 25.04, 24.46, 24.42, 16.84, 16.78, 16.77, 16.68; HRMS (M+Na) calc mass 389.1576, found 389.1592.



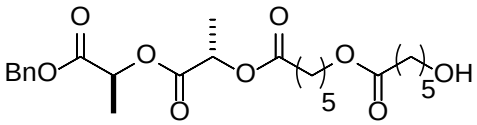
Bn-GCLC. The product was a colorless liquid (2.59 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.17 (s, 2H), 5.05 (q, 1H, J = 7.1 Hz), 4.63 (s, 2H), 4.11 (t, 2H, J = 6.6 Hz), 3.65-3.59 (m, 2H), 2.40 (t, 2H, J = 7.5 Hz), 2.39 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.72-1.52 (m, 8H), 1.49-1.33 (m, 4H), 1.46 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 172.74, 170.94, 167.74, 135.06, 128.62, 128.53, 128. 36, 68.45, 67.07, 65.03, 62.52, 60.58, 33.85, 33.55, 32.24, 28.15, 25.20, 25.08, 24.47, 24.34, 16.94; HRMS (M+Na) calc mass 489.2101, found 489.2144.



Bn-GGCC. The product was a colorless liquid (4.81 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 5H), 5.18 (s, 2H), 4.71 (s, 4H), 4.04 (t, 2H, *J* = 6.6 Hz), 3.64-3.59 (m, 2H), 2.41 (t, 2H, *J* = 7.4 Hz), 2.29 (t, 2H, *J* = 7.4 Hz), 1.71-1.52 (m, 8H), 1.46 (t, 1H, *J* = 1.46), 1.43-1.33 (m, 4H); ^{13}C NMR δ 173.73, 172.69, 167.35, 166.95, 134.84, 128.64, 128.60, 128.41, 67.28, 64.04, 62.59, 61.03, 60.18, 34.18, 33.52, 32.28, 28.25, 25.38, 25.25, 24.63, 24.34; HRMS (M+Na) calc mass 475.1944, found 475.1924.

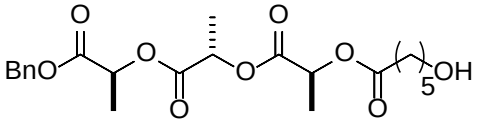


Bn-GGGC. The product was a pale yellow liquid (1.65 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 5.18 (s, 2H), 4.80 (s, 2H), 4.72 (s, 2H), 4.72 (s, 2H), 3.63 (m, 2H), 2.43 (t, 2H, *J* = 7.2 Hz), 1.73-1.65 (m, 2H), 1.60-1.55 (m, 2H), 1.53-1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.85, 167.34, 166.86, 166.60, 134.82, 128.68,128.66, 128.45, 67.39, 62.58, 61.18, 60.69, 60.15, 33.63, 32.24, 25.07, 24.46; HRMS (M+Na) calc mass 419.1318, found 419.1328.

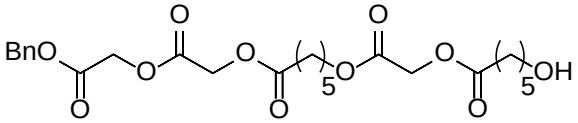


Bn-LLCC. The product was a pale yellow liquid (3.07 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.31 (m, 5H), 5.21-5.04 (m, 4H), 4.04 (t, 2H, *J* = 6.4 Hz), 3.64-3.60 (m, 2H), 2.38 (dt, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.36 (dt, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.29 (t, 2H, *J* = 7.4 Hz), 1.70-1.54 (m, 9H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 6.8 Hz), 1.42-1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.74, 172.94, 170.31, 170.07, 135.10, 128.60, 128.48, 128.22, 69.08,

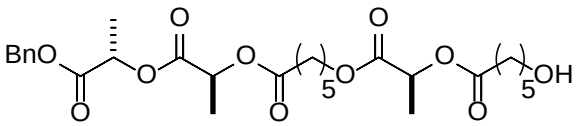
68.21, 67.16, 64.08, 62.64, 34.21, 33.69, 32.31, 28.29, 25.42, 25.27, 24.65, 24.37, 16.78, 16.69; HRMS (M+Na) calc mass 503.2257, found 503.2222.



Bn-LLLC. The product was a colorless liquid (7.91 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.20-5.05 (m, 5H), 3.64-3.59 (m, 2H), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.53 (d, 3H, J = 6.9), 1.51 (d, 3H, J = 7.2 Hz), 1.50 (d, 3H, J = 7.2 Hz), 1.46-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08, 170.43, 169.94, 169.68, 135.04, 128.59, 128.49, 128.68, 69.20, 68.84, 68.15, 67.18, 62.53, 33.74, 32.21, 25.03, 24.42, 16.74, 16.56; HRMS (M+Na) calc mass 461.1788, found 461.1820.

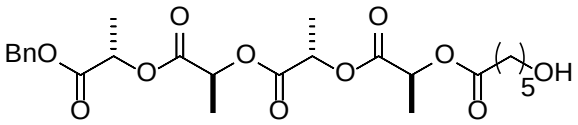


Bn-GGCGC. The product was a colorless liquid (2.87 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.17 (s, 2H), 4.71 (s, 2H), 4.70 (s, 2H), 4.57 (s, 2H), 4.13 (t, 2H, J = 6.6 Hz), 3.64-3.59 (m, 2H), 2.43-2.38 (m, 2H), 1.73-1.62 (m, 6H), 1.60-1.54 (m, 2H), 1.46-1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.94, 172.62, 167.97, 167.34, 166.94, 134.83, 128.62, 128.59, 128.40, 67.27, 65.08, 62.46, 61.02, 60.51, 60.17, 33.66, 33.45, 32.18, 28.09, 25.16, 25.03, 24.45, 24.26; HRMS (M+Na) calc mass 533.2023, found 533.2042.



Bn-LLCLC. The product was a colorless liquid (2.76 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 5H), 5.18 (q, 1H, J = 7.2 Hz), 5.17 (d, 1H, J = 12.3 Hz), 5.11 (d, 1H, J = 12.3 Hz),

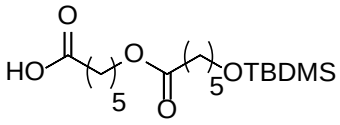
5.07 (q, 1H, J = 7.2 Hz), 5.04 (q, 1H, J = 7.2 Hz), 4.13-4.08 (m, 2H), 3.65-3.59 (m, 2H), 2.42 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.41 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.40 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 2.40 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.1 Hz), 1.72-1.54 (m, 8H), 1.52-1.32 (m, 4H), 1.50 (d, 3H, J = 7.2 Hz), 1.47 (d, 3H, J = 7.2 Hz), 1.45 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.99, 172.88, 170.96, 170.31, 170.06, 135.07, 128.59, 128.47, 128.22, 69.06, 68.44, 68.20, 67.14, 65.06, 62.50, 33.82, 33.62, 32.22, 28.14, 25.19, 25.05, 24.45, 24.30, 16.93, 16.77, 16.67; HRMS (M+) calc mass 552.257063, found 552.256030.



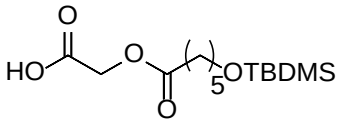
Bn-LLLLC. The product was a colorless liquid (1.48 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.19-5.05 (m, 6H), 3.61 (t, 2H, J = 6.5 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.71-1.60 (m, 2H), 1.59-1.49 (m, 2H), 1.45-1.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08, 170.44, 169.91, 169.73, 169.57, 135.02, 128.59, 128.50, 128.23, 69.24, 68.93, 68.82, 68.14, 67.19, 62.52, 36.58, 33.74, 32.21, 25.03, 24.41, 16.74, 16.72, 16.63, 16.54; HRMS (M+Na) calc mass 533.1999, found 533.2021.

2.4.3 General procedure for benzyl deprotection of diprotected oligomers.

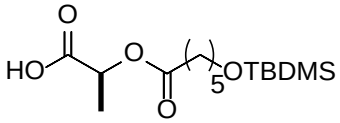
The diprotected oligomers were combined with 10% Pd/C (5% w/w) in dry EtOAc (0.1 M in substrate) and stirred overnight at RT under 1 atm H_2. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The concentrate was purified by chromatography over silica using 5-10% EtOAc in hexanes as the eluent.[15]



CC-SiR3. The product was a colorless liquid (11.43 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (br s, 1H), 4.04 (t, 2H, *J* = 6.6 Hz), 3.58 (t, 2H, *J* = 6.6 Hz), 2.34 (t, 2H, *J* = 7.4 Hz), 2.28 (t, 2H, *J* = 7.6 Hz), 1.68-1.57 (m, 6H), 1.54-1.47 (m, 2H), 1.43-1.33 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.14, 173.84, 63.98, 63.00, 34.31, 33.78, 32.42, 28.29, 25.94, 25.42, 25.40, 24.79, 24.27, 24.27, 18.33, -5.30; HRMS (M+Na) calc mass 383.2230, found 383.2196.

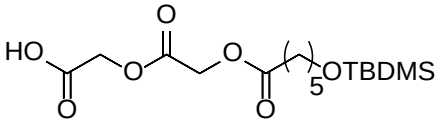


GC-SiR3. The product was a colorless liquid (6.38 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (br s, 1H), 4.63 (s, 2H), 3.59 (t, 2H, *J* = 6.5 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 1.71-1.61 (m, 2H), 1.56-1.47 (m, 2H), 1.41-1.31 (m, 2H), 0.86 (s, 9H), 0.021 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08. 173.00, 62.98, 60.01, 33.69, 32.34, 25.93, 25.27, 24.55, 18.34, -5.31; HRMS (M+Na) calc mass 327.1604, found 327.1585.

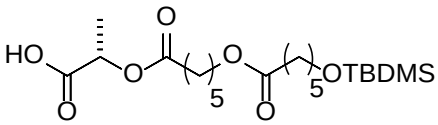


LC-SiR3. The product was a colorless liquid (6.20 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 5.08 (q, 1H, *J* = 7.1Hz), 3.58 (t, 2H, *J* = 6.5 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 1.70-1.60 (m, 2H), 1.56-1.47 (m, 2H), 1.50 (d, 3H, *J* = 7.1 Hz), 1.40-1.33 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.30,

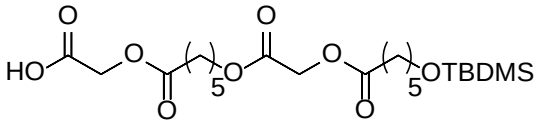
173.09, 67.90, 63.00, 33.86, 32.40, 25.94, 25.60, 25.31, 24.56, 18.34, 16.80, -5.30; HRMS (M+Na) calc mass 341.1760, found 341.1745.



GGC-SiR3. The product was a colorless liquid (4.34 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (br s, 1H), 4.71 (s, 2H), 4.70 (s, 2H), 3.59 (t, 2H, *J* = 6.3 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 1.71-1.61 (m, 2H), 1.56-1.47 (m, 2H), 1.41-1.31 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.04, 171.70, 167.32, 63.02, 60.14, 33.69, 32.32, 25.94, 25.27, 24.55, 18.35, -0.03, -5.31; HRMS (M+Na) calc mass 385.1659, found 385.1638.

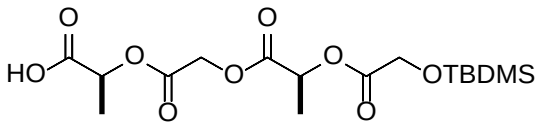


LCC-SiR3. The product was a colorless liquid (4.22 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 5.08 (q, 1H, *J* = 7.2 Hz), 4.04 (t, 2H, *J* = 6.6 Hz), 3.60 (t, 2H, *J* = 6.6 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.38 (dt, 1H, J_1 = 16.0 Hz, J_2 = 7.2), 2.28 (t, 2H, *J* = 7.4 Hz), 1.71-1.58 (m, 6H), 1.55-1.48 (m, 2H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.44-1.38 (m, 2H), 1.37-1.29 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.09, 173.92, 172.87, 68.00, 64.08, 63.16, 34.35, 33.66, 32.27, 28.28, 25.94, 25.43, 24.77, 24.38, 18.37, 16.80, -5.30; HRMS (M+Na) calc mass 455.2441, found 455.2403.

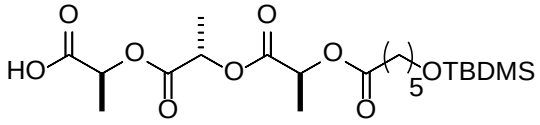


GCGC-SiR3. The product was a colorless liquid (6.10 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (br s, 1H), 4.63 (s, 2H), 4.58 (s, 2H), 4.14 (t, 2H, *J* = 6.6 Hz), 3.59 (t, 2H, *J* = 6.5 Hz),

2.41 (t, 2H, J = 7.2 Hz), 2.40 (t, 2H, J = 7.5 Hz), 1.73-1.60 (m, 6H), 1.54-1.45 (m, 2H), 1.43-1.33 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.25, 172.73, 172.00, 167.98, 65.09, 63.04, 60.60, 60.07, 33.79, 33.49, 32.32, 28.13, 25.94, 25.29, 25.17, 24.61, 24.32, 18.35, -5.31; HRMS (M+Na) calc mass 499.2339, found 499.2328.



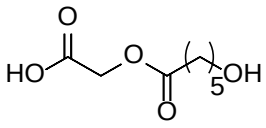
LCLC-SiR$_3$. The product was a colorless liquid (4.15 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (br s, 1H), 5.09 (q, 1H, J = 7.0 Hz), 5.04 (q, 1H, J = 7.0 Hz), 4.13 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.5 Hz), 4.11 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.3 Hz), 3.59 (t, 2H, J = 6.5 Hz), 2.40-2.35 (m (dt), 1H), 2.38 (dt, 1H, J_1 = 12.3 Hz, J_2 = 7.2 Hz), 2.37 (dt, 1H, J_1 = 10.8 Hz, J_2 = 7.6 Hz), 2.36 (dt, 1H, J_1 = 7.4 Hz, J_2 = 15.6 Hz), 1.72-1.59 (m, 6H), 1.56-1.44 (m, 2H), 1.50 (d, 3H, J = 7.0 Hz), 1.45 (d, 3H, J = 7.0 Hz), 1.42-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.03, 173.35, 172.84, 170.93, 68.52, 68.03, 65.07, 63.05, 33.96, 33.66, 32.35, 28.17, 25.94, 25.32, 25.19, 24.61, 24.34, 18.35, 16.94, 16.78, -5.31; HRMS (M+Na) calc mass 527.2652, found 527.2672.



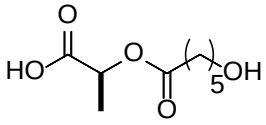
LLLC-SiR$_3$. The product was a colorless liquid (6.92 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (br s, 1H), 5.16 (q, 1H, J = 7.2 Hz), 5.13 (q, 1H, J = 7.2 Hz), 5.08 (q, 1H, J = 7.2 Hz), 3.58 (t, 2H, J = 6.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.7 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.70-1.59 (m, 2H), 1.57-1.46 (m, 5H), 1.56 (d, 3H, J = 7.2 Hz), 1.53 (d, 3H, J = 7.2 Hz), 1.39-1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.21, 173.22, 170.42, 169.68, 68.77, 68.14, 63.01, 33.84, 32.36, 25.93, 25.27, 24.57, 18.33, 16.74, 16.64, 16.58, -5.31; HRMS (M+Na) calc mass 485.2183, found 485.2216.

2.4.4 General procedure for benzyl deprotection of benzyl protected oligomers.

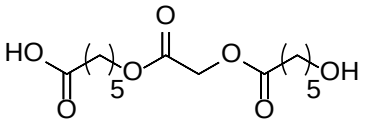
The benzyl protected oligomers were combined with 10% Pd/C (5% w/w) in dry EtOAc and stirred overnight at RT under 1 atm H_2. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The concentrate was redissolved in EtOAc, dried over $MgSO_4$ and filtered through celite. The filtrate was then concentrated *in vacuo*. No further purification was needed.



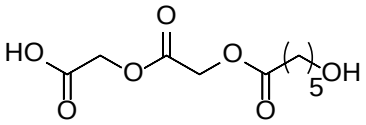
GC. The product was a colorless solid (0.61 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (br s, 2H), 4.63 (s, 2H), 3.65 (t, 2H, *J* = 6.0 Hz), 2.42 (t, 2H, *J* = 7.1 Hz), 1.75-1.65 (m, 2H), 1.63-1.54 (m, 2H), 1.51-1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.05, 171.40, 62.12, 60.11, 33.72, 31.64, 24.48, 24.31; HRMS (M+Na) calc mass 213.0739, found 213.0757.



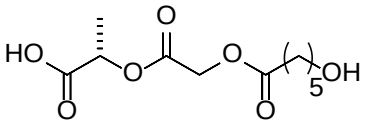
LC. The product was a colorless liquid (0.82 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (br s, 2H), 5.09 (q, 1H, *J* = 7.1 Hz), 3.64 (m, 2H), 2.40 (dt, 1H, J_1 = 15.3 Hz, J_2 = 7.2 Hz), 2.37 (dt, 1H, J_1 = 15.3 Hz, J_2 = 7.1 Hz), 1.72-1.62 (m, 2H), 1.59-1.47 (m, 2H), 1.50 (d, 3H, *J* = 7.1 Hz), 1.45-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.86, 173.21, 68.07, 62.18, 33.82, 31.71, 24,58, 24.30, 16.77; HRMS (M+Na) calc mass 227.0895, found 227.0874.



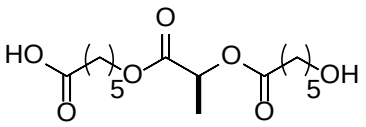
CGC. The product was a colorless solid (0.45 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (br s, 2H), 4.56 (s, 2H), 4.13 (t, 2H, *J* = 6.5 Hz), 3.61 (t, 2H, *J* = 6.5 Hz), 2.40 (t, 2H, *J* = 7.4 Hz), 2.31 (t, 2H, *J* = 7.4 Hz), 1.71-1.51 (m, 8H), 1.44-1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.57, 173.02, 168.01, 65.11, 62.33, 60.54, 33.73, 33.61, 31.94, 28.08, 25.23, 24.96, 24.37, 24.15; HRMS calc mass 304.1522, found 304.1516.



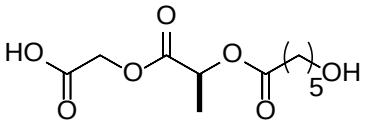
GGC. The product was a colorless solid (1.22 g, 91%). ^{1}H NMR (300 MHz, DMSO) δ 13.22 (br s, 1H), 4.75 (s, 2H), 4.64 (s, 2H), 4.39 (br s, 1H), 3.37 (t, 2H, *J* = 6.3 Hz), 2.38 (t, 2H, *J* = 7.4 Hz), 1.60-1.50 (m, 2H), 1.46-1.28 (m, 4H); ^{13}C NMR (75 MHz, DMSO) δ 172.36, 168.61, 167.51, 61.02, 60.52, 60.07, 33.07, 32.13, 24.91, 24.29; HRMS (M+Na) calc mass 271.0794, found 271.0821.



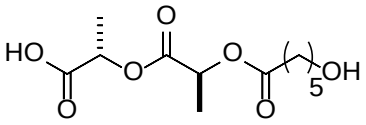
LGC. The product was a colorless liquid (2.14 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (br s, 2H), 5.16 (q, 1H, *J* = 7.2 Hz), 4.72 (d, 1H, *J* = 15.9 Hz), 4.63 (d, 1H, *J* = 15.9 Hz), 3.63 (t, 2H, *J* = 6.5 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 1.72-1.62 (m, 2H), 1.60-1.49 (m, 2H), 1.52 (d, 3H, *J* = 7.2 Hz), 1.47-1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.84, 173.08, 167.48, 69.10, 62.41, 60.34, 33.57, 31.75, 24.88, 24.34, 16.71; HRMS (M+) calc mass 262.105253, found 262.104851.



CLC. The product was a colorless liquid (1.06 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (br s, 2H), 5.04 (q, 1H, *J* = 7.0 Hz), 4.12 (t, 2H, *J* = 6.5 Hz), 3.63 (t, 2H, *J* = 6.5 Hz), 2.38 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 2.33 (t, 2H, *J* = 7.5 Hz), 1.71-1.52 (m, 8H), 1.46-1.33 (m, 4H), 1.45 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.42, 173.09, 171.02, 68.50, 65.07, 62.43, 33.80, 33.73, 32.01, 28.15, 25.27, 24.98, 24.36, 24.20, 16.92; HRMS (M+Na) calc mass 341.1576, found 341.1573.

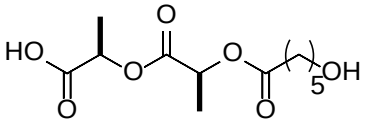


GLC. The product was a colorless liquid (1.19 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (br s, 2H), 5.13 (q, 1H, *J* = 7.2 Hz), 4.73 (d, 1H, *J* = 16.2 Hz), 4.56 (d, 1H, *J* = 16.2 Hz), 3.61 (t, 2H, *J* = 6.5 Hz), 2.38 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.1 Hz), 1.68-1.58 (m, 2H), 1.56-1.49(m, 2H), 1.51 (d, 3H, J = 7.2 Hz), 1.45-1.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.24, 170.46, 170.38, 68.23, 62.33, 60.74, 33.64, 31.60, 24.85, 24.26, 16.74; HRMS (M+Na) calc mass 285.0950, found 285.0974.

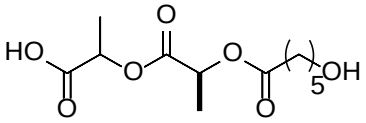


LLC. The product was a colorless liquid (2.08 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (br s, 2H), 5.15 (q, 1H, *J* = 7.2 Hz), 5.09 (q, 1H, *J* = 7.1 Hz), 3.63 (t, 2H, *J* = 6.3 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 2.38 (dt, 1H, J_1 = 15.6 Hz, J_2 = 6.9 Hz), 1.71-1.60 (m, 2H), 1.58-1.48 (m, 8H), 1.45-1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.09, 173.24, 170.40, 68.84, 68.32,

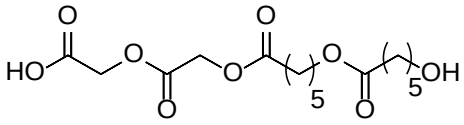
62.44, 33.66, 31.81, 24.89, 24.32, 16.70 (2); HRMS (M+Na) calc mass 299.1107, found 299.1098.



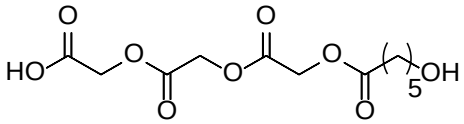
L$_{R}$LC. The product was a colorless liquid (1.41 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 2H), 5.16 (q, 1H, *J* = 7.1 Hz), 5.11 (q, 1H, *J* = 7.1 Hz), 3.63 (t, 2H, *J* = 6.4 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.0 Hz), 1.70-1.62 (m, 2H), 1.60-1.51 (m, 2H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.49 (d, 3H, *J* = 7.2 Hz), 1.43-13.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.77, 173.06, 170.30, 69.07, 68.30, 62.42, 33.76, 31.77, 24.94, 24.33, 16.77, 16.69; HRMS (M+Na) calc mass 299.1107, found 299.1096.



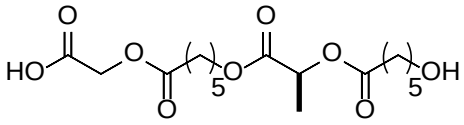
L$_{rac}$LC. The product was a colorless liquid (2.03 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 4H), 5.173 (q, 1H, *J* = 7.1 Hz), 5.168 (q, 1H, *J* = 7.1 Hz), 5.12 (q, 1H, *J* = 7.1 Hz), 5.10 (q, 1H, *J* = 7.1 Hz), 3.64 (t, 2H, *J* = 6.2 Hz), 3.637 (t, 2H, *J* = 6.4 Hz), 2.46-2.32 (m, 4H), 1.71-1.62 (m, 4H), 1.59-1.49 (m, 4H), 1.53 (d, 3H, *J* = 6.8 Hz), 1.52 (d, 3H, *J* = 7.2 Hz), 1.51 (d, 3H, *J* = 6.8 Hz), 1.50 (d, 3H, *J* = 6.8 Hz), 1.46-1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.06, 173.79, 173.20, 173.05, 170.38, 170.33, 69.07, 68.79, 68.34, 68.30, 62.51, 33.78, 33.67, 31.87, 31.83, 24.95, 24.93, 24.34, 16.78, 16.73, 16.70; HRMS (M+Na) calc mass 299.1107, found 299.1108.



GGCC. The product was a white solid (3.12 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (br s, 2H), 4.71 (s, 2H), 4.68 (s, 2H), 4.05 (t, 2H, *J* = 6.4 Hz), 3.65 (t, 2H, *J* = 6.6 Hz), 2.36 (t, 2H, *J* = 7.2 Hz), 2.30 (t, 2H, *J* = 7.6 Hz), 1.72-1.52 (m, 8H), 1.46-1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.12, 172.88, 170.11, 167.35, 64.20, 62.62, 60.75, 60.21, 34.17, 33.56, 31.77, 28.18, 25.39, 25.13, 24.52, 24.39; HRMS (M+Na) calc mass 385.1475, found 385.1493.

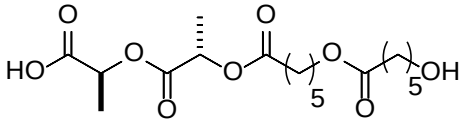


GGGC. The product was a colorless liquid (0.84 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (br s, 2H), 4.79 (s, 2H), 4.72 (s, 2H), 4.70 (s, 2H), 3.65 (t, 2H, *J* = 6.4 Hz), 2.43 (t, 2H, *J* = 7.2 Hz), 1.72-1.67 (m, 2H), 1.60-1.53 (m, 2H), 1.45-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.99, 170.20, 167.42, 166.65, 62.56, 60.93, 60.79, 60.20, 33.58, 31.79, 24.85, 24.40; HRMS (M+Na) calc mass 329.0849, found 329.0854.

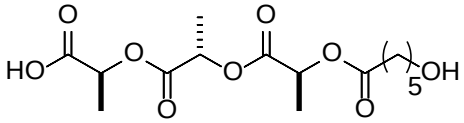


GCLC. The product was a colorless liquid (1.71 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (br s 2H), 5.06 (q, 1H, *J* = 7.1 Hz), 4.62 (s, 2H), 4.13 (dt, 1H, J_1 = 10.8 Hz J_2 = 6.5 Hz), 4.12 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.3 Hz), 3.66 (t, 2H, *J* = 6.5 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.73-1.54 (m, 8H), 1.47-1.36 (m, 4H), 1.46 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.27, 172.84, 68.62, 65.17,

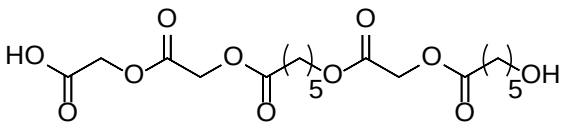
62.45, 60.28, 33.85, 33.57, 31.81, 28.16, 25.10, 24.88, 24.39, 16.90; HRMS (M+Na) calc mass 399.1631, found 399.1662.



LLCC. The product was a colorless liquid (2.05 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (br s, 2H), 5.12 (q, 1H, *J* = 7.1 Hz), 5.08 (q, 1H, *J* = 7.1 Hz), 4.10-4.00 (m, 2H), 3.64 (t, 2H, *J* = 6.6 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 16.0 Hz, J_2 = 7.2), 2.30 (t, 2H, *J* = 7.4 Hz), 1.70-1.55 (m, 8H), 1.52 (d, 6H, *J* = 6.8 Hz), 1.45-1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.05, 173.82, 173.08, 170.24, 68.79, 68.28, 64.18, 62.64, 34.16, 33.75, 31.86, 28.22, 25.42, 25.18, 24.54, 24.45, 16.69 (2); HRMS (M+Na) calc mass 413.1788, found 413.1789.

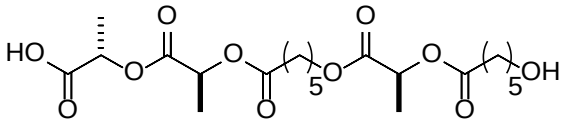


LLLC. The product was a colorless liquid (3.02 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (br s, 2H), 5.21-5.07 (m, 3H), 3.62 (t, 2H, *J* = 6.5 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.1 Hz), 1.71-1.61 (m, 2H), 1.58-1.50 (m, 2H), 1.56 (d, 3H, *J* = 7.2 Hz), 1.53 (d, 3H, *J* = 6.9 Hz), 1,52 (d, 3H, *J* = 7.2 Hz), 1.44-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.19, 173.13, 170.41, 169.63, 68.93, 68.86, 68.21, 62.52, 33.73, 31.93, 24.90, 24.40, 16.75, 16.63 (2); HRMS (M+Na) calc mass 371.1318, found 371.1289.

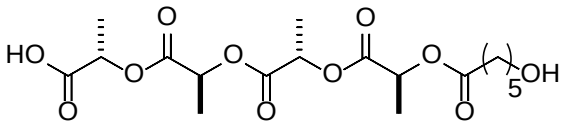


GGCGC. The product was a colorless solid (1.13 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (br s, 2H), 4.71 (s, 2H), 4.68 (s, 2H), 4.60 (s, 2H), 4.15 (t, 2H, *J* = 6.6 Hz), 3.67 (t, 2H, *J* = 6.3

Hz), 2.42 (t, 4H, J = 7.2 Hz), 1.74-1.63 (m, 6H), 1.61-1.54 (m, 2H), 1.49-1.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.20, 172.80, 169.60, 168.24, 167.36, 65.27, 62.37, 60.82, 60.64, 60.28, 33.68, 33.55, 31.66, 28.02, 25.03, 24.71, 24.34, 24.32; HRMS (M+Na) calc mass 443.1529, found 443.1519.



LLCLC. The product was a colorless liquid (1.63 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (br s, 2H), 5.14 (q, 1H, J = 7.2 Hz), 5.06 (q, 1H, J = 7.2 Hz), 5.04 (q, 1H, J = 7.2 Hz), 4.12 (t, 2H, J = 6.6 Hz), 3.64 (t, 2H, J = 6.5 Hz), 2.46-2.29 (m (pair of dt, 2H), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.71-1.51 (m, 14H), 1.49-1.35 (m, 4H), 1.45 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.75, 173.16, 172.98, 171.10, 170.23, 68.79, 68.56, 68.28, 65.16, 62.44, 33.81, 33.67, 31.85, 2 8.10, 25.12, 24.88, 24.38, 24.33, 16.91, 16.71 (2); HRMS (M+Na) calc mass 485.1999, found 485.1994.

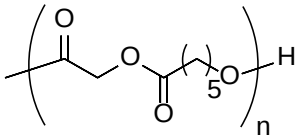


LLLLC. The product was a colorless liquid (1.44 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (br s, 2H), 5.20-5.06 (m, 4H), 3.63 (t, 2H, J = 6.5 Hz), 2.39 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.2 Hz), 1.71-1.61 (m, 2H), 1.58-1.49 (m, 2H), 1.57 (d, 3H, J = 7.2 Hz), 1.55 (d, 3H, J = 7.2 Hz), 1.53 (d, 3H, J = 7.2 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.44-1.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.27, 173.12, 170.43, 169.70, 169.55, 68.96, 68.88,

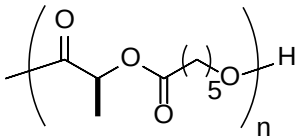
68.19, 62.54, 33.73, 31.95, 24.93, 24.37, 16.75, 16.65 (2), 16.59; HRMS (M+Na) calc mass 443.1529, found 443.1571.

2.4.5 General procedure for the polymerization of the sequenced segmers

The polymerization procedure using DIC/DPTS was adapted from Stupp and coworkers.[82] Under N_2, the unprotected segmer (1 equiv.) and DPTS (0.2 equiv.) were dissolved in CH_2Cl_2 (3M with respect to segmer unless otherwise noted) and cooled to 0 ºC. DIC (1.5 equiv.) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum.

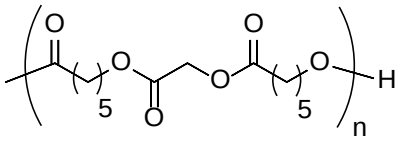


Poly GC. The product was a white solid (0.57 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2H), 4.14 (t, 2H, *J* = 6.5 Hz), 2.41 (t, 2H, *J* = 7.4 Hz), 1.73-1.61 (m, 4H), 1.45-1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73, 167.87, 65.10, 60.53, 33.53, 28.14, 25.21, 24.33; SEC (THF): M_n – 26.4 kDa, M_w – 37.5 kDa, PDI – 1.42.

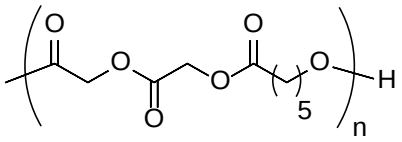


Poly LC. The product was a colorless glass (0.37 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (q, 1H, *J* = 7.1 Hz), 4.12 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.8 Hz), 4.11 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 2.38 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.72-1.60 (m, 4H), 1.46 (d, 3H, *J* = 7.1 Hz), 1.42-1.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.76,

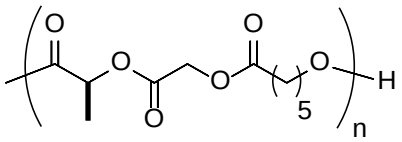
170.85, 68.43, 65.05, 33.70, 28.16, 25.23, 24.33, 16.95; SEC (THF): M_n – 37.9 kDa, M_w – 53.9 kDa, PDI – 1.42.



Poly CGC. The polymerization was carried out in DMF. The product was a white, tacky glass (1.19 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 2H), 4.12 (t, 2H, *J* = 6.6 Hz), 4.03 (t, 2H, *J* = 6.6 Hz), 2.40 (t, 2H, *J* = 7.4 Hz), 2.27 (t, 2H, *J* = 7.5), 1.72-1.56 (m, 8H), 1.43-1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.44, 172.76, 167.86, 65.11, 64.07, 60.50, 34.00, 33.56, 28.25, 25.36, 25.32, 24.44, 24.37; SEC (THF): M_n – 18.3 kDa, M_w – 25.8 kDa, PDI – 1.41.

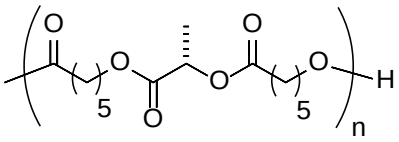


Poly GGC. The polymerization was carried out in a 3:1 mixture of CH_2Cl_2 and DMF. The product was an off white, tacky glass (0.80 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.65 (s, 2H), 4.14 (t, 2H, *J* = 6.6 Hz), 2.41 (t, 2H, *J* = 7.4 Hz), 1.72-1.60 (m, 4H), 1.44-1.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 167.34, 167.08, 65.32, 61.02, 60.17, 33.43, 28.06, 25.15, 24.25, 23.46 (DIU); SEC (THF): M_n – 24.9 kDa, M_w – 36.2 kDa, PDI – 1.45.

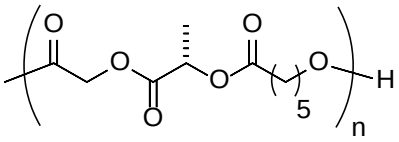


Poly LGC. The product was an off white tacky glass (1.34 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (q, 1H, *J* = 7.0 Hz), 4.71 (d, 1H, *J* = 16.2 Hz), 4.61 (d, 1H, *J* = 16.2), 4.11 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 4.11 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.5 Hz), 2.40 (t, 2H, *J* = 7.4 Hz), 1.71-1.59

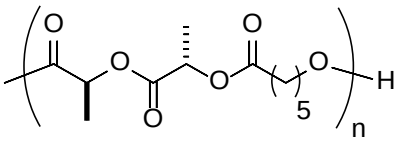
(m, 4H), 1.47 (d, 3H, J = 7.0 Hz), 1.43-1.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.58, 170.03, 167.24, 69.27, 65.25, 60.25, 33.43, 28.07, 25.16, 24.26, 16.85; SEC (THF): M_n – 27.3 kDa, M_w – 39.6 kDa, PDI – 1.45.



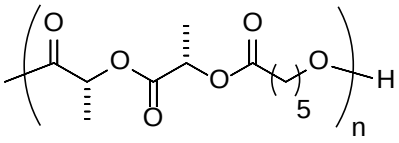
Poly CLC. The product was a colorless glass (0.42 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (q, 1H, J = 7.0 Hz), 4.11 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 4.10 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 4.03 (t, 2H, J = 6.8 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 2.36 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 2.28 (t, 2H, J = 7.5 Hz), 1.71-1.57 (m, 8H), 1.45 (d, 3H, J = 7.0 Hz), 1.42-1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 172.77, 170.83, 68.43, 65.05, 64.11, 34.05, 33.75, 28.30, 25.41, 25.35, 24.48, 24.48, 24.40, 16.95; SEC (THF): M_n – 26.9 kDa, M_w – 37.1 kDa, PDI – 1.38.



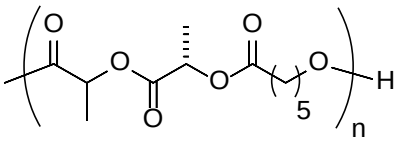
Poly GLC. The product was an off white tacky glass (0.38 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (q, 1H, J = 7.2 Hz), 4.74 (d, 1H, J = 15.9 Hz), 4.53 (d, 1H, J = 15.9 Hz), 4.13 (t, 2H, J = 6.6 Hz), 2.38 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.70-1.60 (m, 4H), 1.54 (d, 3H, J = 7.2 Hz), 1.43-1.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.70, 170.28, 167.18, 68.16, 65.26, 60.91, 33.58, 28.08, 25.16, 24.25, 16.35; SEC (THF): M_n – 29.4 kDa, M_w – 42.3 kDa, PDI – 1.44.



Poly LLC. The product was a colorless glass (1.19 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (q, 1H, *J* = 7.2 Hz), 5.08 (q, 1H, *J* = 7.2 Hz), 4.11 (t, 1H, *J* = 6.6 Hz), 4.10 (t, 1H, *J* = 6.6 Hz), 2.38 (t, 1H, *J* = 7.5 Hz), 2.36 (t, 1H, *J* = 7.4 Hz), 1.70-1.58 (m, 4H), 1.53 (d, 3H, *J* = 7.2 Hz), 1.49 (d, 3H, *J* = 7.2 Hz), 1.45-1.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.78, 170.26, 170.22, 69.08, 68.22, 65.22, 33.63, 28.16, 25.20, 24.30, 16.84, 16.77; SEC (THF): M_n – 30.8 kDa, M_w – 43.8 kDa, PDI – 1.4.

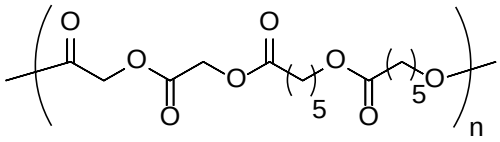


Poly L$_R$LC. The product was a colorless liquid (0.51 g, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (q, 1H, *J* = 7.0 Hz), 5.09 (q, 1H, *J* = 7.2 Hz), 4.12 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 4.10 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 2.37 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 1.68-1.62 (m, 4H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.46 (d, 3H, *J* = 7.2 Hz)1.40-1.35 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.55, 170.05, 170.00, 69.17, 68.34, 65.22, 33.66, 28.11, 25.23, 24.33, 16.89, 16.86; SEC (THF): M_n – 30.7 kDa, M_w – 41.5 kDa, PDI – 1.35.

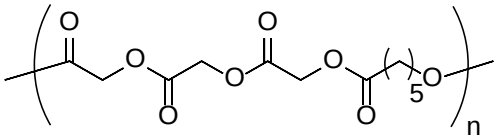


Poly L$_{rac}$LC. The product was a colorless liquid (1.08 g, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 515-5.057 (m, 4H), 4.15-4.07 (m, 4H), 2.38 (dt, 2H, J_1 = 15.6 Hz, J_2 = 6.9 Hz), 2.36 (dt, 2H, J_1 = 15.0 Hz, J_2 = 6.9 Hz), 1.68-1.61 (m, 8H), 1.53 (d, 3H, *J* = 6.6 Hz), 1.50 (d, 3H, *J* = 6.6 Hz),

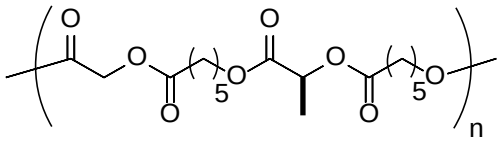
1.49 (d, 3H, *J* = 6.0 Hz), 1.46 (d, 3H, *J* = 7.2 Hz), 1.40-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.83, 172.80, 172.54, 172.50, 170.27, 170.22, 170.04, 170.00, 69.18, 69.05, 68.34, 68.20, 65.24, 65.22, 65.19, 33.66, 33.61, 28.14, 28.11, 25.23, 25.22, 25.20, 25.18, 24.32, 24.29, 24.28, 16.89, 16.86, 16.84, 16.76; SEC (THF): M_n – 25.7 kDa, M_w – 33.6 kDa, PDI – 1.31.



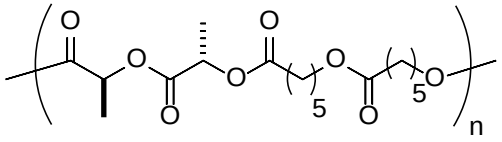
Poly GGCC. The product was a an offwhite solid (2.46 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.65 (s, 2H), 4.14 (t, 2H, *J* = 6.6 Hz), 4.03 (t, 2H, *J* = 6.6 Hz), 2.41 (t, 2H, *J* = 7.6 Hz), 2.28 (t, 2H, *J* = 7.6 Hz), 1.71-1.58 (m, 8H), 1.42-1.31 (m, 4H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 173.46, 172.64, 167.34, 167.08, 65.37, 64.08, 61.01, 60.17, 33.99, 33.50, 28.25, 28.12, 25.36, 25.31, 24.43, 24.33; SEC (THF): M_n – 33.8 kDa, M_w – 54.0 kDa, PDI – 1.60.



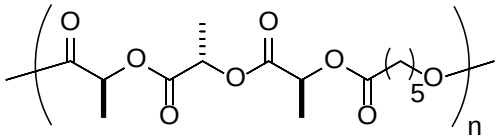
Poly GGGC. The product was a white solid (0.63 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 2H), 4.71 (s, 2H), 4.66 (s, 2H), 4.14 (t, 2H, *J* = 6.6 Hz), 2.41 (t, 2H, *J* = 7.4), 1.71-1.61 (m, 4H), 1.43-1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.59, 167.24, 166.96, 166.59, 65.37, 61.17, 60.66, 60.15, 33.43, 28.07, 25.16, 24.25; SEC (THF): M_n – 22.4 kDa, M_w – 32.4 kDa, PDI – 1.44.



Poly GCLC. The product was a colorless glass (0.81 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (q, 1H, *J* = 7.1 Hz), 4.58 (s, 2H), 4.14 (t, 2H, *J* = 6.5 Hz), 4.12 (t, 2H, *J* = 6.3 Hz), 2.41 (t, 2H, *J* = 7.5 Hz), 2.38 (dt, 1H, J_1 = 15.9 Hz, *J* = 7.8 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.73-1.60 (m, 8H), 1.45 (d, 3H, *J* = 7.1 Hz), 1.45-1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73, 172.71, 68.47, 65.12, 65.03, 60.55, 33.71, 33.57, 28.18, 25.25, 25.24, 24.35, 16.95; SEC (THF): M_n – 20.6 kDa, M_w – 28.6 kDa, PDI – 1.39.

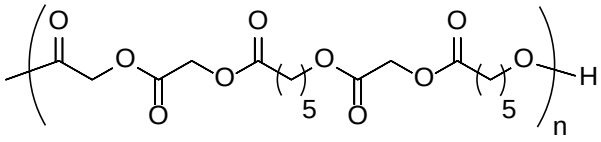


Poly LLCC. The product was a colorless glass (1.28 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13-5.04 (m, 2H), 4.14-4.07 (m, 2H), 4.02 (t, 2H, *J* = 6.4 Hz), 2.37 (t, 1H, J_1 = 15.6 Hz, J_2 = 6.8 Hz), 2.36 (dt, 1H, J_1 = 15.6 Hz, J_2 = 6.6 Hz), 2.26 (t, 2H, *J* = 7.4 Hz), 1.68-1.57 (m, 8H), 1.52 (d, 3H, *J* = 7.2 Hz), 1.48 (d, 3H, *J* = 7.2 Hz), 1.41-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.41, 172.84, 170.26, 170.20, 69.04, 68.16, 65.20, 64.09, 33.99, 33.63, 28.25, 28.14, 25.35, 25.27, 24.43, 24.33, 16.81, 16.74; SEC (THF): M_n – 40.6 kDa, M_w – 65.7 kDa, PDI – 1.62; Anal. calcd for HO-$(C_{11}H_{10}O_4)_n$-H: C, 58.05; H, 7.58. Found: C, 58.12; H, 7.47.

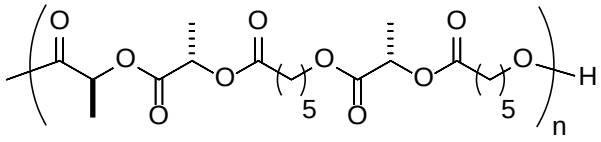


Poly LLLC. The product was an off white, tacky glass (1.69 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (q, 1H, *J* = 7.2 Hz), 5.09 (q, 1H, *J* = 7.2 Hz), 5.07 (q, 1H, *J* = 7.2 Hz), 4.10 (dt,

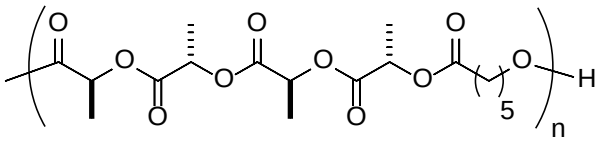
1H, J_1 = 10.5 Hz, J_2 = 6.8 Hz), 4.09 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 2.37 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.35 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.69-1.59 (m, 4H), 1.56 (d, 3H, J = 7.2 Hz), 1.52 (d, 3H, J = 7.2 Hz), 1.47 (d, 3H, J = 7.2 Hz), 1.43-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.80, 170.32, 170.08, 169.65, 69.17, 68.80, 68.17, 65.23, 33.56, 28.09, 25.13, 24.25, 16.78, 16.72, 16.63; SEC (THF): M_n – 24.0 kDa, M_w – 34.9 kDa, PDI – 1.45.



Poly GGCGC. The product was a white semisolid (0.68 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.66 (s, 2H), 4.57 (s, 2H), 4.15 (t, 2H, J = 6.5 Hz), 4.13 (t, 2H, J = 6.5 Hz), 2.413 (t, 2H, J = 7.5 Hz), 2.407 (t, 2H, J = 7.4 Hz), 1.72-1.60 (m, 8H), 1.44-1.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73, 172.60, 167.87, 167.34, 167.09, 65.33, 65.08, 61.03, 60.53, 60.18, 33.51, 33.46, 28.12, 28.09, 25.18, 24.31, 24.28; SEC (THF): M_n – 21.7 kDa, M_w – 31.7 kDa, PDI – 1.46.



Poly LLCLC. The product was a colorless, tacky glass (1.11 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19-4.99 (m, 3H), 4.17 (m, 4H), 2.46-2.28 (m, 4H), 1.71-1.59 (m, 8H), 1.53 (d, 3H, J = 6.9 Hz), 1.49 (d, 3H, J = 6.9 Hz), 1.45 (d, 3H, J = 6.6 Hz), 1.41-1.33 (m , 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.83, 172.74, 170.84, 170.28, 170.23, 69.06, 68.44, 68.20, 65.22, 65.05, 33.68, 33.61, 28.15, 25.20, 24.32, 24.29, 16.94, 16.84, 16.76; SEC (THF): M_n – 49.1 kDa, M_w – 70.1 kDa, PDI – 1.43.



Poly LLLLC. The product was a white, tacky glass (0.89 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18-5.03 (m, 4H), 4.10 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 4.09 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.6 Hz), 2.37 (dt, 1 H, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 2.35 (dt, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz), 1.69-1.59 (m, 4H), 1.57 (d, 3H, J = 6.9 Hz), 1.56 (d, 3H, J = 7.2 Hz), 1.53 (d, 3H, J = 7.2 Hz), 1.48 (d, 3H, J = 7.2 Hz), 1.41-1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.80, 170.34, 170.07, 169.73, 169.55, 69.22, 68.93, 68.81, 68.17, 65.25, 33.57, 28.10, 25.14, 24.26, 16.78, 16.74, 16.64 (2); SEC (THF): M_n – 35.8 kDa, M_w – 50.2 kDa, PDI – 1.40.

3.0 DETERMINING SEQUENCE FIDELITY IN REPEATING SEQUENCE POLY(LACTIC-*CO*-GLYCOLIC ACIDS)

The work described in this chapter includes contributions from Jian Li, Han H. Liu, and Michael A. Washington and Joseph A. Giesen and Scott M. Grayson from Tulane University and is accepted for publication

3.1 INTRODUCTION

3.1.1 Sequence and effects on properties

Sequence control in synthetic polymers is relatively underdeveloped despite the overwhelming evidence from biological polymers and hybrid polymers such as peptide conjugates or DNA-conjugates that sequence can be used to tune properties.[1,2,41,42,100,101] The significant synthetic challenges in controlling monomer sequence are responsible for the paucity of data about the influence of sequence on polymer properties.[7,8] Most of what is known about the effect of sequence on copolymer properties comes from the study of polymers with a more synthetically accessible alternating sequence, random copolymers with varying average block lengths, and block/multi-block copolymers.[46-50] That being said, the dramatic differences in properties that

can be accessed within this limited list of motifs suggests that sequence engineering at a monomer-by-monomer level has a tremendous potential for impact.

There have recently been increasing efforts to explore sequence in copolymers.[7,8] There have been, for example, efforts to introduce and improve synthetic approaches to creating monomer order including methods based on chain-growth,[51-54,102,103] step-growth,[15-17,53,55-61] templating,[62-65] ring-opening,[21,30,104-106] and linear iterative processes.[107-115] Researchers have also begun to explore more deeply the effect of sequence on properties in a variety of materials such as conjugated materials,[12,13,103] non-biological polymers designed to display a variety of side-chains as seen in peptides,[111,112,116,117] biodegradable poly(α-hydroxy esters),[15-19] and polymers in which side-chain placement and spacing are of primary interest.[11,51,53,118-121] As sequenced copolymers become more prevalent, the development of analytical methodologies for both verifying and reading sequences and stereosequences is of increasing importance.[122-132]

3.1.2 Calculation of sequence fidelity in copolymers

In this chapter we seek to explore the concept of sequence fidelity (SF) as it pertains to periodic or repeating sequence copolymers with the long-term goal of correlating SF with bulk properties. This issue is important because it is likely that some level of error will be present in any sequenced copolymer prepared and, furthermore, that properties of the polymer will depend on the types and degree to which errors are present. For a polymer with a targeted sequence of $(ABC)_n$, for example, mistakes wherein an ABC unit is replaced by an AB or BCA unit (or both) may be present in a particular sample. We define the SF in this context as the ratio of error-free to total polymer repeat units (eq. 1) and the error rate (ER) as in eq. 2. The SF and ER are related in that the sum of all units, both correct and errors, will total 100% (eq. 3). Sequence

fidelity differs from the universally recognized concept of "purity" in that the definition accounts for mistakes that do not change the stoichiometry or chemical purity of the sample, e.g. when an ABC unit is replaced with a BCA unit.

$$\text{SF} = \frac{\text{error-free polymer repeat units}}{\text{total polymer units}} \times 100\% \qquad (1)$$

$$\text{ER} = \frac{\text{specific type of error unit}}{\text{total polymer units}} \times 100\% \qquad (2)$$

$$\text{SF} = 100 - \sum \text{ER} \qquad (3)$$

We focused our SF studies on repeating sequence poly(lactic-*co*-glycolic acid)s or PLGAs that were previously reported by our group.[15] This system was chosen because our group has considerable experience in preparing and characterizing these polymers and because we have a long term interest in understanding the role of sequence in determining the degradation behavior of these materials due to their potential for use in bioengineering applications. We have, for example, reported the preparation of a large number of sequenced polymers: **poly LG**, **poly LLG**, **poly LL$_R$G**, etc., where L = the naturally occurring S enantiomer of lactic acid; L$_R$ = the R enantiomer; and G = glycolic acid). In studies of these repeating sequence copolymers, we have found important correlations between properties and monomer order. It was demonstrated that the order of the monomers dictates the hydrolysis behavior and that sequenced copolymers retain their morphology while losing molecular weight in a nearly linear fashion.[18,19] These results are of interest because we have found that our sequenced PLGAs exhibit dramatically different behavior from random PLGAs which have been widely used for drug-delivery, cell-scaffolding, and degradable coatings for a variety of devices.[24,133]

Sequence and sequence mistakes in copolymers have been previously examined using ^{1}H NMR spectroscopy and mass spectrometry. NMR spectroscopy has long been established as a useful tool for characterizing monomer order and stereochemistry in copolymers. When chemical

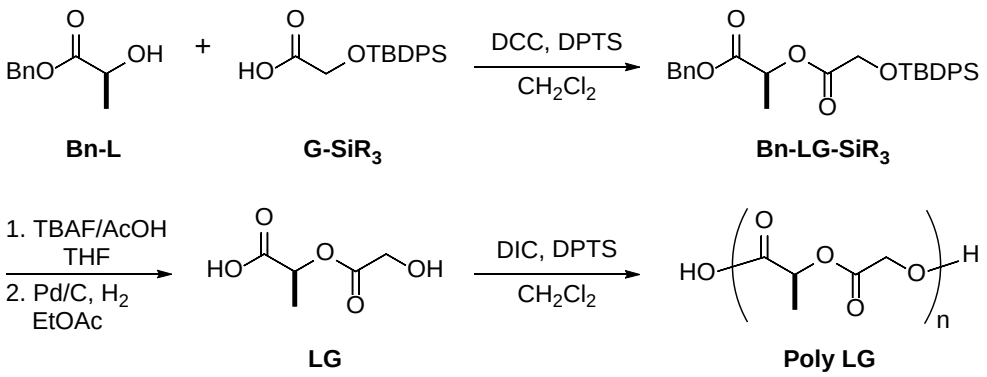
shifts for particular sequences are known and when the shift differences between polyads of interest are resolved, the relative ratios can be determined by integration.[124,127,130,132,134,135] Sequence has increasingly been analyzed, particularly for complex polymers like peptides, using mass spectrometry.[122-132,136] Key to these a majority of these analyses, however, is the monodispersity of the parent ion, and the controlled fragmentation of the biopolymer into component pieces prior to and/or during the experiment. Using sophisticated algorithms, these fragments are then computationally reassembled into their original structure and sequence. The mass spectrometric analysis of synthetic polymers is more complicated in most cases due to the molecular weight dispersity inherent to most polymers. Indeed, soft ionization techniques, such as matrix-assisted laser desorption/ionization (MALDI) are usually employed to avoid the data complexity that results from fragmentation of complex mixtures or multiply charged species. Under these conditions, singly charged ions for the unfragmented polymer chains are resolved and can be analyzed to determine monomer distributions, repeating unit masses, end group identities, and information about architecture.[122,126,137-143]

Herein, we report the use of non-optimized, one-dimensional matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to both characterize and quantify sequence in periodic PLGAs and we compare the accuracy of the quantitation with NMR spectroscopy.

3.2 RESULTS AND DISCUSSION

3.2.1 SAP of sequenced PLGAs

The synthesis of all materials was carried out using our previously developed method for the preparation of repeating sequence copolymers bearing L-lactic acid (L_S), R-lactic acid (L_R), racemic lactic acids (L_{rac}), glycolic acid (G), and other hydroxy acids.[15-18,21] The method, designated Segmer Assembly Polymerization (SAP), involves an initial preparation of segmers (sequenced oligomers) by Steglich esterification. The di-protected dimer **Bn-LG-SiR$_3$**, for example, comes from the coupling reaction of the orthogonally protected monomers **Bn-L** (Bn = benzyl) and **G-SiR$_3$** (SiR_3 = *tert*-butyl-di-phenylsilyl) (Scheme 5). Treatment with TBAF/AcOH, followed by hydrogenolysis over Pd/C gives the unprotected segmer **LG**. The difunctional segmer is then polymerized using a step-growth approach in the presence of diisopropylcarbodiimide (DIC) and 4-(dimethylamino) pyridinium *p*-toluenesulfonate (DPTS) to afford the sequenced copolymer **Poly LG**. All materials described herein (**Table 4**) were prepared using variations of this strategy. With the exception of the "errormers" whose preparation is detailed below all materials have been previously reported and are described elsewhere.[15]



Scheme 5. Synthesis of **Poly LG** by SAP.

3.2.2 MALDI-ToF analysis of repeating sequence PLGAs

In analyzing PLGA samples that we have prepared using SAP, much can be learned from MALDI-ToF MS. As an example, the spectrum of a particular sample of **Poly LL*R*G**, which exhibited a significant number of errors, is analyzed (**Figure 11**). With a mass separation corresponding to a single LLG segmer, the major peaks in the mass spectrum correlate with the targeted sequence (stereochemistry can only be differentiated in special cases by MALDI-ToF MS analysis[144,145] so the *R* subscript is omitted in the rest of this discussion). The presence of this dominant pattern is consistent with that which would be expected from the SAP assembly of **LLG** units. It is notable that all chains in this sample were cyclic. The tendency of esters to cyclize is well known and we find cyclics dominate in the SAP-produced species, despite the relatively high concentrations employed for the polymerizations (3 M), at least in 1000-5000 m/z weight range which is typically observable under the experimental conditions used.[146]

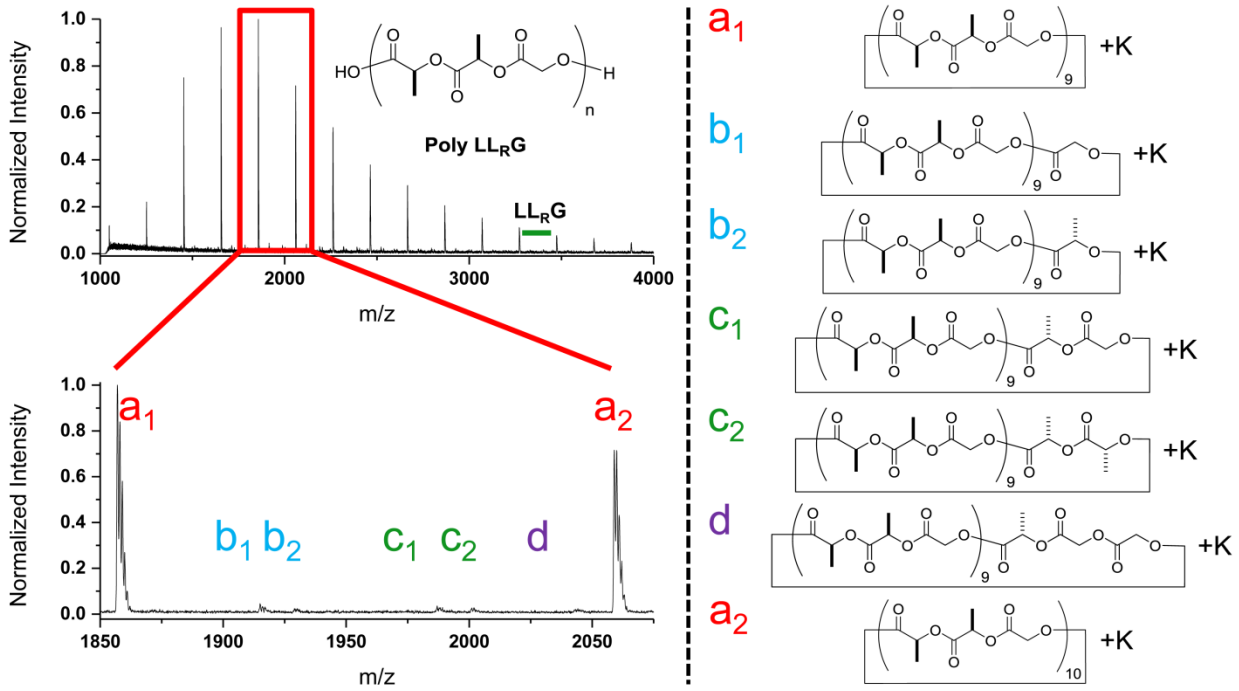


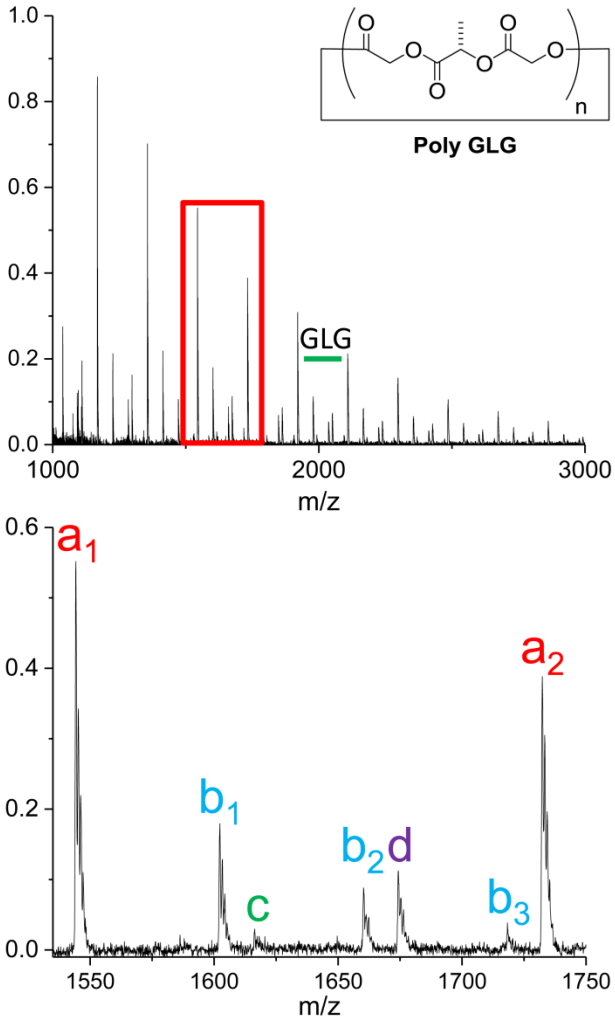
Figure 11. MALDI-ToF mass spectrum of **Poly LL*R*G** (top left), **Poly LL*R*G** expansion from 1850-2075 m/z (bottom left) and error analysis and assignment MALDI-TOF-MS peaks of **Poly LL*R*G** (right). Data acquired on Voyager-DE PRO MALDI-ToF MS system.

Focusing on the 1850-2075 m/z region, isotopic peak envelopes that correspond to cyclic $(LLG)_n$ where n = 9 and 10 (a_1 & a_2) can be identified. Between these two error-free chains, peaks corresponding to +LG, +LL, and +LGG errors are found (c_1, c_2, d_1). These minor series repeat between each set of major series peaks.

It is important to note, however, that the identification of the extra units present in the series does not inherently give any information about their source or distribution in the chain. We cannot know, for example, whether the +LG error is due to the lack of an L unit from a single segmer LLG repeat unit or if the perceived error is the result of two errors, +L and +G. Moreover, we cannot rule out cancelling errors, e.g., a chain that encodes the same number of +L and +LG errors will be read as having no errors. Although MS/MS analysis would be expected to provide some additional information about error distribution, the analysis of fragments from polymers with short periodic sequences of two monomers and no fragmentation preferences is

challenging due to the limited number of possible masses. For example, a 5-mer fragment arising from an L-G cleavage with no error would have the structure LLGLL while a 5-mer fragment formed from L-L cleavage with a +L error, LLLGL, will have the same molecular weight. With this limitation in mind we have chosen to focus our attention on the one-dimensional spectra which for periodic copolymers encode substantial information about sequence fidelity.

A second polymer example, **Poly GLG**, upon MALDI-ToF MS analysis also exhibited multiple identifiable errors (**Figure 12**). Investigating the region from 1540-1750 m/z the main isotopic peaks correspond to cyclic $(GLG)_9$ and $(GLG)_{10}$. Error peaks between the two main peaks correspond to cyclic $(GLG)_9$ with additional units of +G, +L, +GG, +GL, and +GGG. These errors have a greater intensity compared with those observed for the **Poly LL$_R$G** at the same degree of polymerization suggesting that the sequence fidelity of this sample is lower.



	m/z	Sequence
a_1	1544.2	$(GLG)_8\ K^+$
b_1	1602.3	$(GLG)_8$+G K^+
c	1616.4	$(GLG)_8$+L K^+
b_2	1660.2	$(GLG)_8$+GG K^+
d	1674.2	$(GLG)_8$+GL K^+
b_3	1718.3	$(GLG)_8$+GGG K^+
a_2	1732.3	$(GLG)_9\ K^+$

Figure 12. MALDI-ToF mass spectrum of **Poly GLG** (top), **Poly GLG** expansion from 1540-1750 m/z (middle), and error analysis and assignment of MALDI-ToF MS peaks of **Poly GLG** expansion spectrum (bottom). Data acquired on a Voyager-DE PRO MALDI-ToF MS system.

It is important to note that for all MALDI-ToF MS data that are analyzed in this chapter, we have chosen to focus on the areas of the spectra that exhibit the greatest total intensity for both

perfect chains and chains containing errors, independent of the molecular weight of the sample. *No effort was made to optimize the data collection to ensure or to determine if the spectrum obtained was representative of the absolute molecular weight distribution of the sample analyzed.* The rationale for this approach and the validity will be discussed in more detail after the data are presented.

In addition to identifying the types of errors, we found in the course of characterizing a wide range of sequenced copolymers, that the MALDI-ToF mass spectra also appeared to give quantitative information about the error frequency. The spectra of the dimeric alternating copolymer **Poly LG**, for example, demonstrate the variable nature of the errors present in particular samples. Focusing on the same region (ca. 1590-1870 m/z) for three independently prepared polymers, we observed a batch with an error rate below the detection threshold, another with only +L errors, and one were both +L and +G errors were present (**Figure 13**).

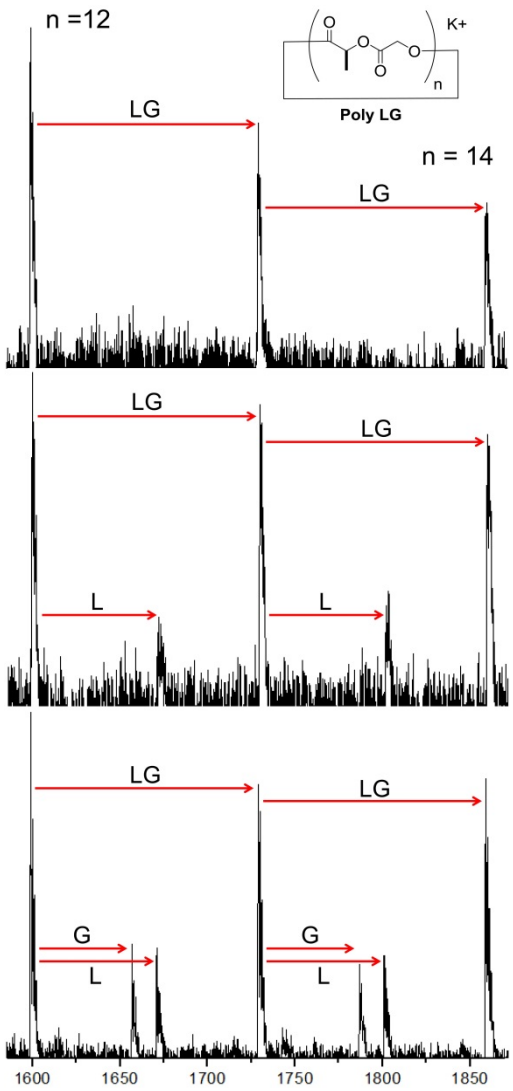


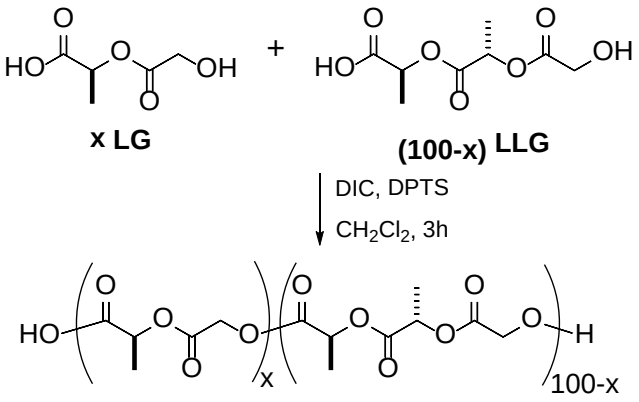
Figure 13. Expansion from 1590-1870 m/z of sample to sample variance in sequence error of **Poly LG.** Data acquired on a Voyager-DE PRO MALDI-ToF MS system.

Given the existence of nearly "error-free" spectra and the lack of non-cyclic species which would be expected if fragmentation was occurring in the spectrometer, we can be confident that fragmentation during analysis does not contribute significantly to the production of observed errors. Moreover, from a mechanistic perspective, the existence of error-free batches also indicated that the errors are not a necessary result of the polymerization reaction itself. We conclude, therefore, that under the reaction conditions that we use, the unintended mistakes result primarily from the contamination of monomer reagents, e.g., L units in LG monomers. Such

errors can arise either from inadequate purification of the monomers prior to polymerization and/or by decomposition of the monomers through hydrolysis or transesterification events, which are both known issues for alkyl esters of this type.[147,148]

3.2.3 Synthesis and analysis of sequenced PLGA "errormers"

Although in analyzing the MALDI-ToF MS data, it is straight-forward to the compare the intensities of the chains with and without errors, the accuracy of such a comparison was uncertain given the challenges inherent in obtaining representative chain distributions in MALDI-ToF spectra.[149] We reasoned, however, that the MALDI signal response for a narrow weight range should give a crudely quantitative comparison, as the polyesters compared are all cyclic (same architecture and end groups), and have the same number of ester groups along the backbone. This hypothesis was tested—and was confirmed—by the preparation and characterization of a series of sequenced PLGAs with controlled error rates, termed "errormers" (**Scheme 6**).



Scheme 6. Synthesis of PLGA errormers with controlled introduction of sequence errors

Synthetically, samples with predominantly LG repeating units and variable amounts of +L errors, similar to the sample which gave the middle spectrum in **Figure 13**, were targeted. A

series of such polymers was produced by combining variable ratios of LLG and LG segmers under the standard step-growth conditions (**Scheme 6**). This method was used rather than the conceptually more simple approach of adding small amounts of L units to a polymerization of LG units because LG and LLG units should exhibit similar coupling environments for both the hydroxyl (L) and carboxylic (G) ends (see below for the validation of this hypothesis). For analysis purposes the LLG unit is, however, regarded as contributing a normal LG unit and a +L error unit. As such, the polymer produced via a molar combination of 0.126 mmol of LLG and 7.06 mmol LG, will include 0.126 mmol L_{err} and 7.06 + 0.126 = 7.186 mmol of LG units. The mol% of L_{err} (ER) is, therefore, calculated as 1.7% (0.126 mmol L_{err}/(7.186 mmol LG + 0.126 mmol L_{err}) = 0.0172). Since there is only one type of error present, the predicted SF would be 1-ER or 98.3%.

Characterization of the polymer errormers by SEC (calibrated to PS standards) showed a molecular weight (M_n) range from ~16-31 kDa (**Table 3**). The dispersities (Đ) of the copolymers ranged from 1.3-1.6 which is consistent with our previous results using this polymerization method.[15-17] MALLS analysis of previously synthesized sequenced PLGAs showed that the absolute molecular weight of these polymers is 50-90% of the SEC weight, depending on the sequence copolymer.[15]

Table 3. Molecular weight data of sequenced PLGAs doped with an L unit error

Polymer	M_n (kDa)[a]	M_w (kDa)[a]	Đ[b]
0% errormer	15.9	25.2	1.6
1.7% errormer	30.7	40.7	1.3
2.4% errormer	17.2	28.0	1.6
5.0% errormer	21.5	31.7	1.5
8.4% errormer	14.0	22.4	1.6
11.6% errormer	18.5	29.0	1.6

a) Determined by SEC in THF relative to PS standards.
b) M_w/M_n.

The polymers were first analyzed by ^{1}H NMR spectroscopy and the error was quantified by integration (**Figure 14a** Standards for comparison are readily available in our laboratory as we have prepared a wide range of sequences including **Poly LLG**. Moreover, we have established that the ^{1}H NMR spectra of these sequenced PLGAs are highly resolved and extremely sensitive to sequence such that errors are likely to be identifiable. In this case, the resonances for the +L error units which have a local pentad sequence of LG*L*LG were clearly distinguishable from those of L units embedded in the base sequence LG*L*GL. In particular, one half of the methine quartet associated with error L's could be resolved from the region containing the base L methine signal. Analysis (including the subtraction of the other half of the partly overlapping error L quartet) gave the error estimations shown in **Table 4**. As can be seen, there is good but not perfect correlation between the stoichiometric feed percentages used and the errors determined by integration.

Table 4. Sequenced PLGA errormer data

Polymer	Mol % L_{err}[a]	Mol % L_{err}:LG[b]	NMR[c] error rate	Error Rate MS % (ER)[d]	Sequence Fidelity MS % (SF)[d]
0% errormer	0.0	0:100	trace	trace	~100.0
1.7% errormer	1.7	1:57.8	2.3	1.2	98.8
2.4% errormer	2.4	1:40.7	4.1	2.5	97.5[e]
5.0% errormer	5.0	1:19	5.4	5.5	94.5
8.4% errormer	8.4	1:10.9	11.3	11.0	89.0
11.6% errormer	11.6	1:7.6	13.3	13.4	86.6

a) (mol L_{err})/(mol L_{err} + mol $LG_{from\ LLG}$ + mol LG) in feed b) (LG mol%)/(L_{err} mol%) in feed c) Calculated from ^{1}H NMR integrations of L_{err} chemical shifts d) Calculated from MALDI-ToF mass spectra; acquired on a Bruker ultrafleXtreme MALDI ToF system e) MS acquired on a Voyager-DE PRO MALDI-ToF system (lower resolution and sensitivity).

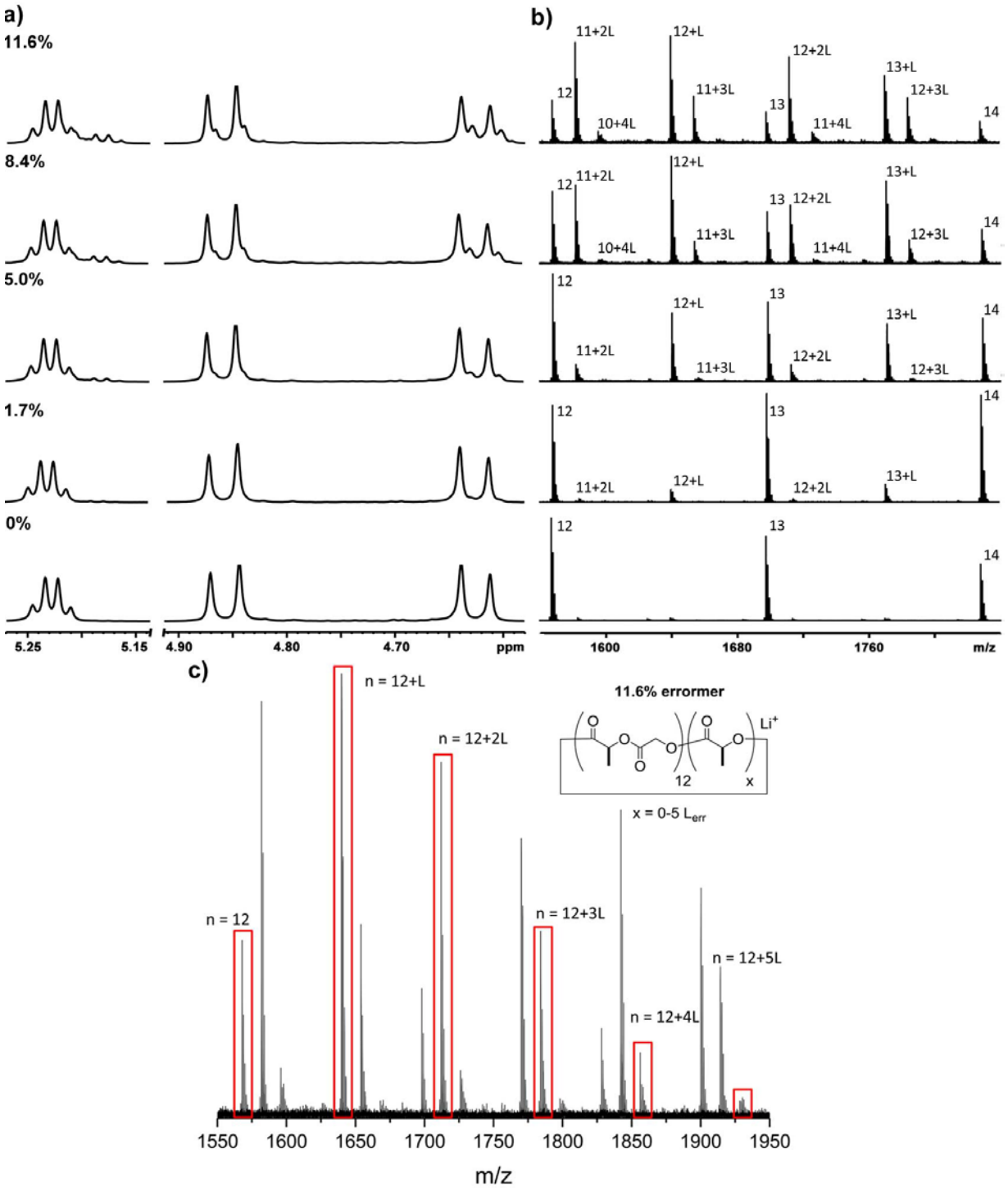


Figure 14. a) Comparison of the 600 MHz ^{1}H NMR spectra b) Expansion (1560-1840 m/z) of MALDI-ToF mass spectra of 0, 1.7, 5.0, 8.4, and 11.6% errormers with the formula *cyclic*-$(LG)_n(L)_m$ + Li^+ . Error-free chains are labeled with the repeat number *n* and chains with errors according to their repeat number and number of "L" errors, n + m(L). Acquired on a Bruker ultrafleXtreme MALDI ToF system. c) Expansion (1550-1950 m/z) of MALDI-ToF mass spectrum of the 11.6% errormer. Note: 2.4% errormer is not shown as the MS data were acquired on a lower resolution/sensitivity instrument.

The polymer samples were also analyzed by MALDI-ToF mass spectrometry. Not surprisingly, the molecular weight distributions observed in the mass spectrum (M_n 1000 to 3000 m/z) differ significantly from those obtained by SEC (16-31 kDa) both due to the known overestimation of the molecular weights as calibrated to polystyrene[15] and the inherent bias for shorter chains in the laser desorption process used to volatilize polymer chains for the mass spectrometry analysis.[149] That being said, neither of these issues is expected to affect dramatically the types or quantities of errors observed, since the error pattern is redundant for each chain length and since errors are expected to be statistical in their distribution (Note: this assumption is tested and found to be true, *vide infra*). The only requirement for analysis is that amongst the data collected there exists one or more chain lengths in which both the error-free chain and all significant error-containing chains have sufficient intensity to allow for a meaningful comparison.

The MALDI-ToF MS data for the errormer set exhibits the expected pattern of error peaks and peaks for chains with more than one error as a function of both chain length and error rate. Focusing on the 1550-1840 m/z region which represents DP = 12-14 (**Figure 14b**), the qualitative progression can be clearly seen. First, it is clear that the 0% errormer is not strictly error-free. Trace amounts of +L errors (and some +G errors) were observed. As we progress to the 1.7% errormer, peaks associated with +L are clearly increased and a small peak for +2L can also be identified. As the error rate increases the percentage of chains with errors increases and peaks for increasing errors per chain are observed. In the 11.6% errormer, peaks associated extra +L errors dominate over those from the error-free LG chains and peaks for error rates of up to +5L errors per chain (1927 m/z) have significant intensity (**Figure 14c**). It should be noted that the data for the 2.4% errormer is not included in the figure since it was collected on a mass

spectrometer with significantly lower resolution/sensitivity. A plot of this mass spectrum can be found in the appendix (**Figure 89**). The 2.4% errormer data were, however, included in the calculations.

To calculate sequence fidelity for these MS data, we used the general approach described in equation 4. The expression SF(n) represents the sequence fidelity for a chain with a repeat number of *n*. The total number of repeat units present with no error, $n[(\text{polymer})_n]$ will be divided by the total intensity of all peaks associated with all chains with the base degree of polymerization *n*. This approach generates a fidelity that should be independent of chain length and easily adaptable to a polymer sample that has more than one source of error.

$$\mathrm{SF}(n) = \frac{n(polymer)_n}{n(polymer)_n + \sum_{i,x}(errormer_x)_i} \qquad (4)$$

$$\mathrm{SF}(n) = \frac{n(LG)_n + \sum_{x=1-4}(n-x)(L_{err})_n}{n[(LG)_n + \sum(L_{err})_n]} \qquad (5)$$

Applied to the specific data collected on the LG errormer series, the SF(n) can be expressed as shown in equation 5. The total "correct LG" units in the numerator was calculated as the number of correct units present in the chains with no errors as $n(\text{LG})_n$ plus the correct units present in the chains with mistake +L units. As stated earlier the added LLG units are treated for the purposes of analysis as two units, L + LG. The denominator represents the total repeat units present, where each LG or L is considered a unit. For example, a chain with the following sequence, LG-LG-LG-**L**-LG-LG-LG-**L**-LG would be counted as having an *n* of 7 and would contribute 7 correct LG units and two L error units to the total. For the quantities $(\text{LG})_n$, and $(\text{L}_{err})_n$ in the expression, the sum of the intensities of all peaks in the isotopic envelope was used. It should be noted that we verified independently that intensities tracked closely with integrations for these spectra (**Figure 15**).

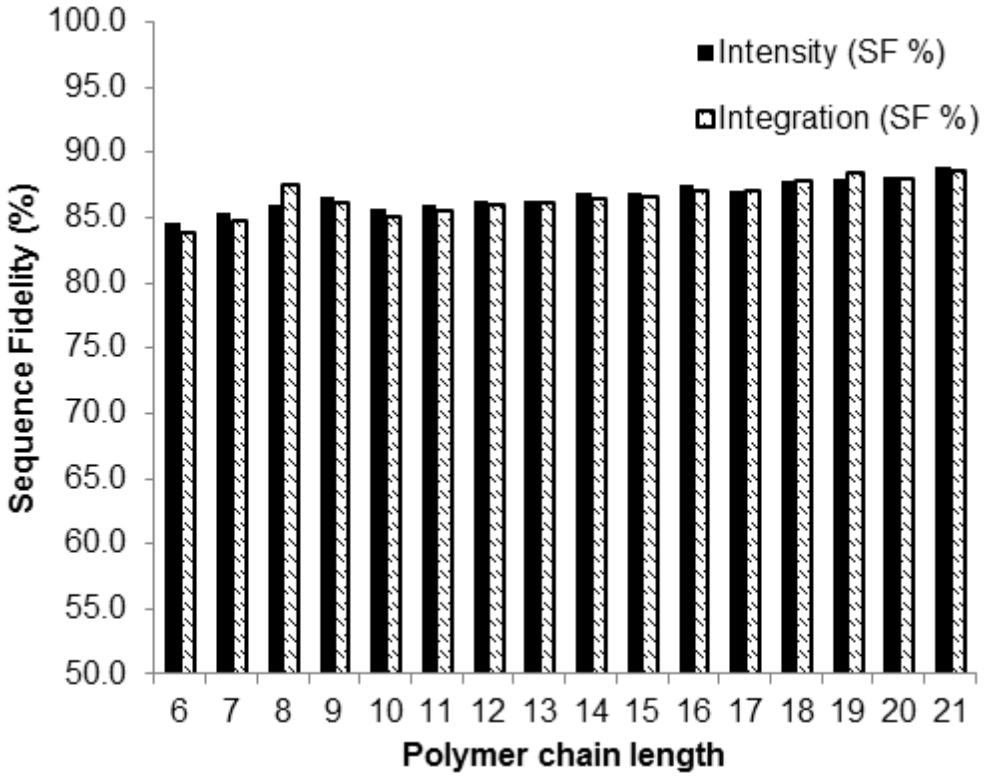


Figure 15. Comparison of calculated sequence fidelity (SF) of poly LG 11.6% errormer's chain lengths from 6-21 obtained from intensity and integration values from the same mass spectrum.

For each errormer sample the SF(n) was calculated for a range of chain lengths. The range of *n* selected for each sample was determined by the signal-to-noise ratio (S/N) of the strongest peak for each series—analysis was only carried out if this peak exhibited an intensity greater than 10% relative to the base peak for the entire spectrum. The intensity, sequence fidelity, and percent error data for each errormer were determined and are located in the appendix (**Table 15-18**). The percent error determined for each chain length in each errormer can be found in **Table 5**.

Table 5. Percent error calculated for each polymer chain length for each errormer determined by MALDI-ToF-MS

	Error Frequency (=1-SF) (%)				
Chain Length	1.7%-errormer[a]	2.4%-errormer[b]	5.0%-errormer[a]	8.4%-errormer[a]	11.6%-errormer[a]
6	2.1	---	6.4	11.7	15.3
7	2.2	---	6.6	11.5	14.6
8	2.5	3.2	5.6	11.2	14.1
9	1.9	3.2	5.5	10.5	13.4
10	1.7	3.0	5.6	11.6	14.3
11	1.1	2.6	5.5	11.0	14.0
12	1.3	2.2	5.3	10.8	13.7
13	1.3	2.6	5.6	11.0	13.7
14	1.2	2.6	5.4	11.1	13.1
15	1.1	2.3	5.3	10.7	13.1
16	1.2	---	---	10.7	12.5
17	1.3	---	---	---	13.0
18	1.3	---	---	---	12.2
19	---	---	---	---	12.0
20	---	---	---	---	11.8
21	---	---	---	---	11.1

[a]Hi-res data obtained on a Bruker ultrafleXtreme MALDI TOF/TOF system b) low-res data obtained on a Voyager-DE PRO MALDI-TOF-MS

We had anticipated that the fidelities/errors determined in this fashion would be independent of chain length but found instead that there was a small dependence on degree of polymerization. A particularly clear example of the observed behavior can be found in the analysis of the 11.6% errormer (**Figure 16**). We propose that the regime in which the fidelity is independent of *n* represents the best estimate because it is in this region that the relative intensities for the peaks of both the error-free and errormer chains are similar, which facilitates accurate comparison. When the peaks are similar in intensity the overestimation of the contribution of peaks with low S/N is minimized. Consistent with this hypothesis, the data for all samples skews towards a low SF at low chain lengths and high SF for longer chain lengths. It should be noted that at lower error rates, data show only the skew towards low SF at low chain lengths. The higher chain length deviation was not observed in the range of *n* whose signals were sufficiently intense for analysis.

It was possible in these cases, nevertheless, to identify a region in which chain length dependence was minimized to identify as the error estimate (**Figure 17**, **Table 5**).

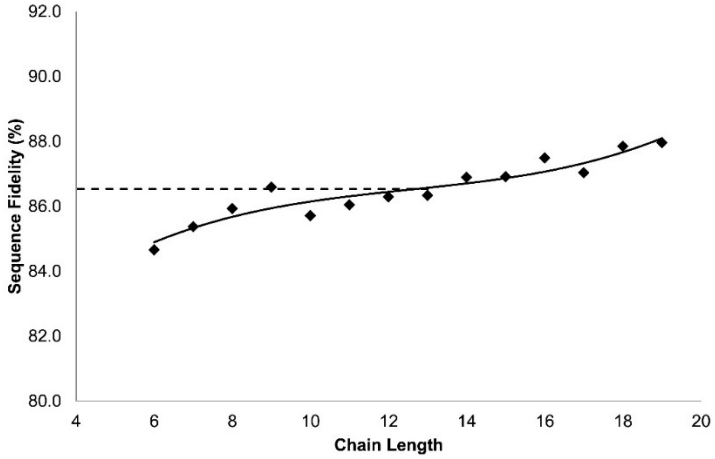


Figure 16. Sequence fidelity (SF %) of each chain length in 11.6% L doped Poly LG errormer. The dotted line is the average sequence fidelity of the flat region of the curve (86.5%).

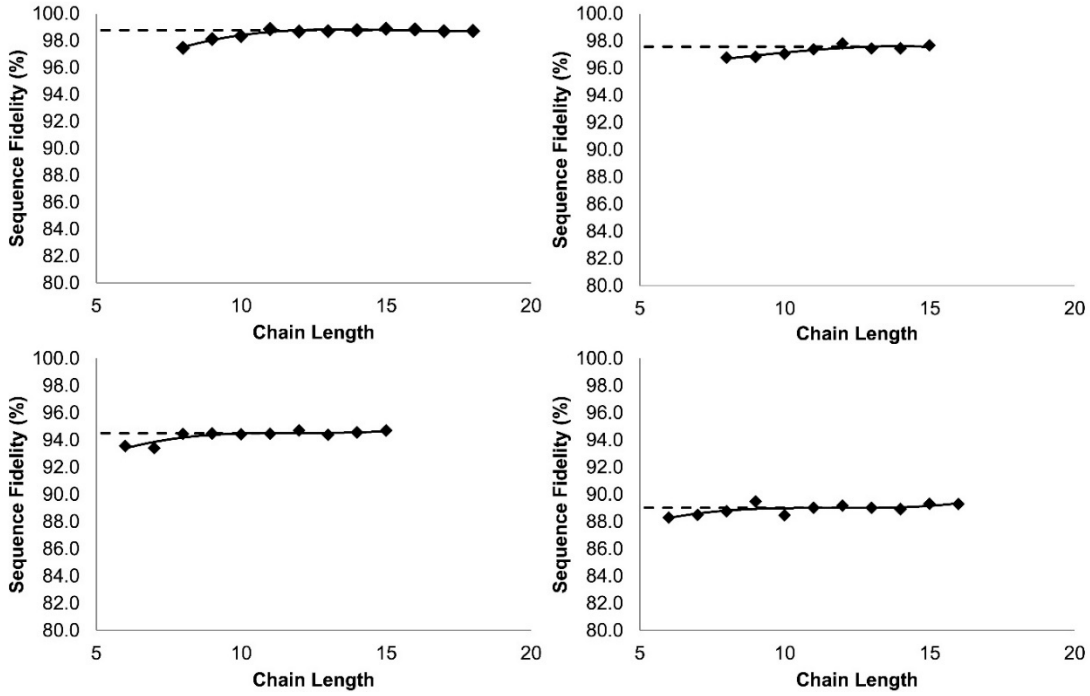


Figure 17. Sequence fidelity (SF %) of each chain length in Poly LG errormers (where the dotted line is the average sequence fidelity of the flat region of the curve. a) 1.7% errormer (98.8%), b) 2.4 % errormer (97.6%), c) 5.0% errormer (94.5%), d) 8.4% errormer (89.0%).

Overall, both NMR spectroscopy and MALDI-ToF mass spectrometry provided a reasonable estimate of the sequence fidelity, although there were some interesting differences (**Figure 18**,

Table 6). NMR spectroscopy, which we expected to be quite accurate in this particular case due to the clean resolution and ease of identification of the signals due to errors, consistently suggested that the error rate was higher than what would be expected from the feed of LLG monomer. The MALDI-ToF MS analysis concurs with the NMR analysis at error rates greater than 5% but estimates that the error is either similar to or below the feed ratio for samples with lower error rates.

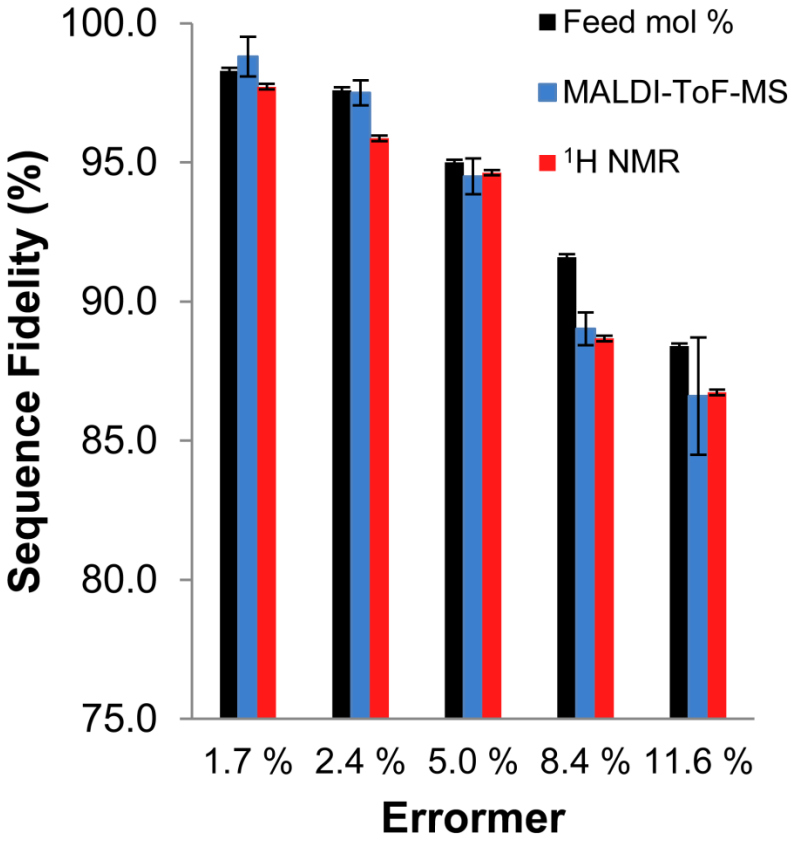


Figure 18. Sequence fidelity of L-doped **Poly LG** errormers calculated from mole percent monomer in the feed (gray), MALDI-ToF MS (blue), and ^{1}H NMR spectroscopy (red).

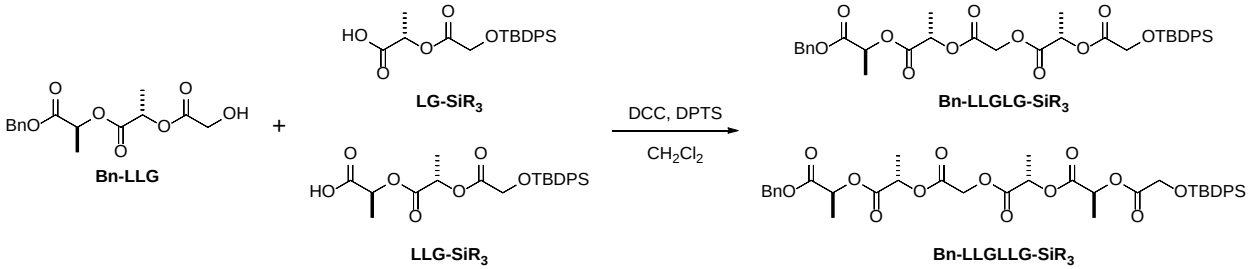
Table 6. Sequence fidelity and percent error of errormers determined by MALDI-ToF MS

Polymer	Sequence Fidelity (%)[a]	Percent Error (%)[a]
0% errormer	100	0.0
1.7% errormer	98.8	1.2
2.4% errormer	97.5	2.5
5.0% errormer	94.5	5.5
8.4% errormer	89.0	11.0
11.6% errormer	86.1	13.4

[a]Sequence fidelity and percent error were determined by MALDI-ToF MS.

3.2.4 Segmer relative reactivity study

We determined by running a separate control experiment that the relative reactivities of the two monomers LLG and LG were similar. Orthogonally protected monomers of **Bn-LLG**, **LLG-SiR$_3$**, and **LG-SiR$_3$** were combined and subjected to coupling conditions (**Scheme 7**). The silyl monomers were used in combined excess to ensure free competition. The ^{1}H NMR spectrum of the mixture of products **Bn-LLGLLG-SiR$_3$** and **Bn-LLGLG-SiR$_3$** was analyzed in the 5.4-5.1 ppm range (**Figure 19**). The 1:1 integration of the diastereotopic G-methylene signals associated with the two products, suggest that there is no monomer preference. Although we did not carry out the reverse experiment (**Bn-LG** + **LLG-SiR$_3$** + **LG-SiR$_3$**), the lack of preference in the initial competition experiment combined with our long experience coupling these and other related monomers suggests that any differences in reactivity are extremely small.



Scheme 7. Coupling reaction of **Bn-LLG**, **LLG-SiR$_3$**, and **LG-SiR$_3$** to determine if there is a monomer reactivity preference. The silyl protected monomers were added in excess (combined) compared to that of **Bn-LLG**.

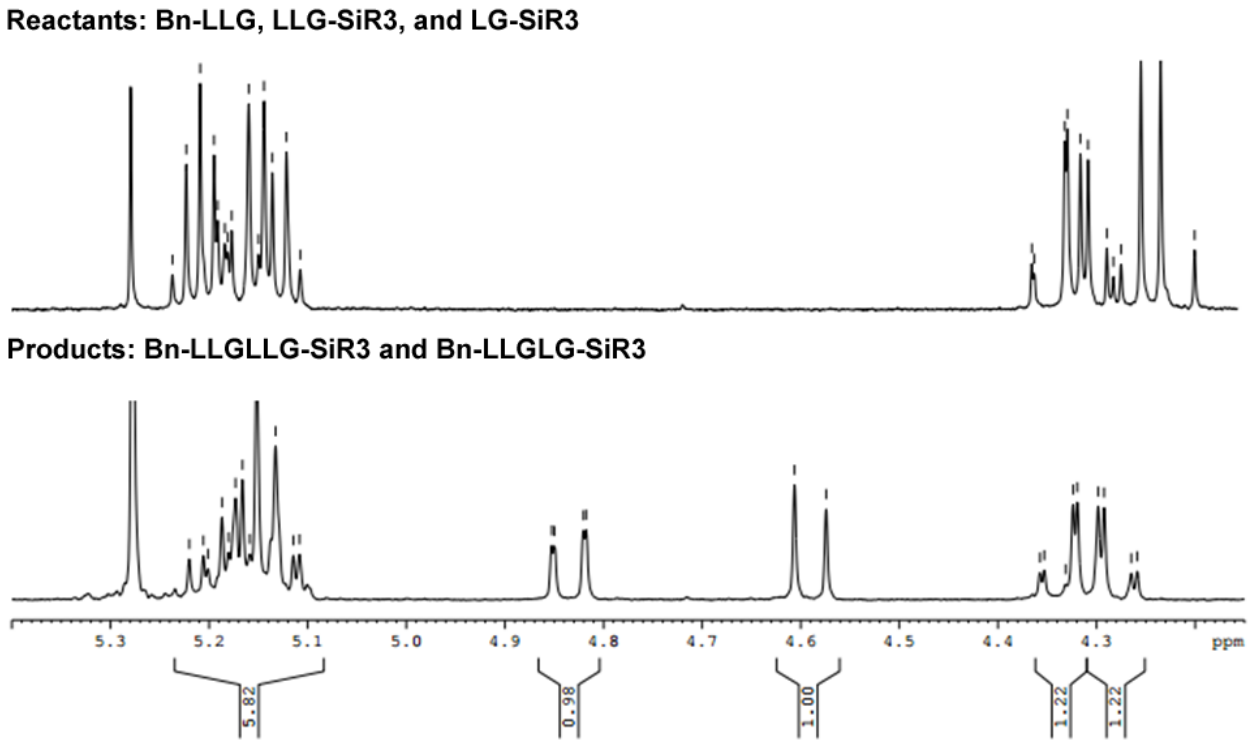


Figure 19. Reactivity preference study of **Bn-LLG** with **LLG-SiR$_3$** and **LG-SiR$_3$**. Top: ^{1}H NMR spectrum of the reactants **Bn-LLG**, **LLG-SiR$_3$**, and **LG-SiR$_3$**. Bottom: the mixture of products **Bn-LLGLLG-SiR$_3$**, **Bn-LLGLG-SiR$_3$**. In collaboration with Michael Washington.

The finding that there is no preference for incorporation of LLG units into the polymer, suggests that either our analysis methods inherently overestimate error (especially at higher error rates where we would expect the greatest accuracy), or that the fidelity of the polymers does not match the feed for some other reason. While the answer to this question has not yet been definitively determined, we currently hypothesize that the isolation process, which involves a standard precipitation of the polymer in methylene chloride into methanol, enriches the less soluble high molecular weight fraction with chains containing more LLG.

In considering the generality of the MALDI-ToF MS methodology for analyzing other periodic copolymers, three criteria must be met to ensure that the integrations can be compared quantitatively: 1) the error units must not have a dramatically different ionization efficiency than the monomers they replace; 2) the end groups of all chains being integrated should be the same; and 3) the molecular weight of a chain and a chain with errors must be relatively close to

minimize molecular-weight induced differences in volatilization. Finally, it must be acknowledged that the error levels that are quantifiable will depend on the range of molecular weights that exist in the sample and/or can be successfully detected. Very small error rates will be difficult to accurately quantify in very short chains and large error rates will be challenging to interpret in long chains because the abundance of error-free chains will approach zero.

3.3 CONCLUSIONS

We have used both ^{1}H NMR spectroscopy and MALDI-ToF mass spectrometry to analyze copolymers containing repeating sequences of lactic and glycolic acids and we have used these methods to determine the types of errors and the sequence fidelity. In examining a series of polymers prepared with targeted error rates, both NMR and MALDI-ToF methods provided similar estimates of sequence fidelity. That being said, despite the proven utility of NMR spectroscopy for characterizing sequence, mass spectrometry may, in many cases, prove more useful for error analysis. In addition to providing structural information about the nature of the error, MS clearly differentiates systematic error from contamination, because the errors are shown as a function of chain length—longer chains show a systematic increase in errors/chain. NMR analysis cannot easily distinguish between inter- and intramolecular contamination. Moreover, assigning the specific nature of an error by NMR spectroscopy is not always possible, especially if standards do not exist, and error peaks may overlap with other resonances such that quantitation is not possible. Finally, the presence of low molecular weight oligomers (or other contaminants) complicates the analysis of the NMR data as those peaks cannot be differentiated easily from peaks due to sequence mistakes.

3.4 EXPERIMENTAL

3.4.1 Materials

All experiments were carried out in oven-dried glassware under an atmosphere of N_2 using standard Schlenk line techniques. N,N'-dicyclohexylcarbodiimide (DCC) was purchased from Oakwood Chemical and used without further purification. Pd/C (10%) was purchased from Alfa Aesar. Triethylamine was distilled under nitrogen from calcium hydride. Methylene chloride (CH_2Cl_2, Fisher), ethyl acetate (EtOAc, Sigma Aldrich) and (THF, Fisher) were purified by passage over neutral activated alumina. The reagents 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS),[82] silyl (-SiR_3, *tert*-butyl-di-phenylsilyl) and benzyl (Bn) protected monomers, unprotected monomers and polymers were prepared according to previously published protocols.[15,16,21]

3.4.2 Characterization

^{1}H NMR spectroscopy. ^{1}H (500 and 600 MHz) NMR spectra were recorded using Bruker spectrometers in $CDCl_3$ and calibrated to the solvent peaks of δ 7.24 ppm.

Size exclusion chromatography. Molecular weights and dispersities were obtained on a Waters GPC (THF) with Jordi 500, 1000, and 10000 Å divinyl benzene columns, and refractive index detector (Waters) was calibrated to polystyrene standards.

Differential scanning calorimetry. Differential scanning calorimetry was performed with a TA Instruments Q200 on polymers containing **L** and **G** monomers. Samples were prepared by dissolving in CH_2Cl_2, dropcasted into aluminum pans, and put under vacuum overnight. The

samples were annealed at 85 ºC for 3 h. Each run had a heating and cooling rate of 10 ºC/min. T_g's were recorded in the second heating cycle.

MALDI-ToF MS. Low-res MALDI-ToF MS spectra were obtained on a Voyager-DE PRO instrument with a 337 nm N_2 laser. An accelerating voltage of 20 kV was applied. The mass spectra of the polymers were obtained in the reflection mode (500 shots). The polymers were dissolved in THF to yield a concentration of 1 mg mL^{-1}. Potassium trifluoroactetate was prepared by addition of trifluoroacetic acid to potassium hydroxide. Potassium trifluoroacetate (KTFA) was used as the cationization agent and was dissolved in THF to form a 1 mg mL^{-1} solution. The matrix utilized was *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malonitrile (DCTB) in THF as a 40 mg mL^{-1} solution. The three solutions were combined in a ratio of 1:1:1.5 (polymer solution: matrix solution: KTFA solution) and allowed to mix for 1 h. The solution was then was drop cast onto a 100-well MALDI plate and allowed to dry for 45 min before analysis. The spectra were analyzed using the OriginLab software package. High-res MALDI-ToF MS spectra were obtained in collaboration with Bruker Daltonics on a Bruker ultrafleXtreme MALDI ToF system. The samples were analyzed in the reflector positive mode. The polymers were dissolved in THF to yield a concentration of 10 mg mL^{-1}. Dithranol was used as the matrix and was prepared at 20 mg mL^{-1} in THF and LiTFA (1 mg mL^{-1}) was used as the cationization agent. The samples were prepared by combining the matrix, polymer sample, and LiTFA in a 10:5:1 ratio. The solution was drop cast onto a MALDI plate and allowed to dry. The spectra were analyzed using the Bruker flexAnalysis software package. The centroid peak detection algorithm was used.

3.4.3 Errormer Synthesis

0%L$_{err}$. Bn-LG (1.7 g, 7.1 mol) and 10% Pd/C (0.08 g, 5% w/w) were combined in dry EtOAc (70 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (1.0 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (q, J = 7.2 Hz, 1H), 4.29 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.5 Hz, 1H), 1.57 (d, J = 7.5 Hz, 3H).

Poly LG (0% errormer polymer). **LG** (1.0 g, 6.8 mmol) and DPTS (0.26 g, 0.9 mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.25 ml) with stirring at RT under N_2. DIC (1.6 mL, 10.2 mmol) was added dropwise and the reaction was allowed to stir for 3h. The polymerization mixture was dissolved in a minimum amount of CH_2Cl_2 and precipitated into MeOH (75 ml). The solid was redissolved and then precipitated in MeOH (75 ml) and dried under vacuum to yield a colorless solid (0.34 g, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23 (q, J = 7.0 Hz, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1 H), 1.57 (d, J = 6.6 Hz, 3H); SEC (THF relative to PS standards) M_n: 15.9 kDa, M_w: 25.2 kDa, Đ: 1.6; T_g: 47 °C, T_m: 114 °C.

1.7%L$_{err}$. Bn-LG (1.7 g, 7.0 mol), **Bn-LLG** (0.04 g, 0.12 mol) and 10% Pd/C (0.09 g, 5% w/w) were combined in dry EtOAc (70 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (0.98 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ LG: 5.24 (q, J = 7.2 Hz, 1H), 4.29

(d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.5 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H), LLG: 5.22 (q, J = 7.2 Hz).

1.7% errormer (ratio 1:58 LLG:LG). **LG** (0.97 g, 6.5 mmol), **LLG** (0.025 g, 0.11 mmol), and DPTS (0.26 g, 0.9 mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.15 ml) with stirring at RT under N_2. DIC (1.5 ml, 9.8 mmol) was added dropwise and the reaction was allowed to stir for 3h. The polymerization mixture was dissolved in a minimum amount of CH_2Cl_2 and precipitated into MeOH (75 ml). The solid was redissolved and then precipitated in MeOH (75 ml) and dried under vacuum to yield a colorless solid (0.50 g, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ Poly LG: 5.23 (q, J = 7.0 Hz, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 1.68 (d, J = 7.2 Hz, 3H), LLG Errors: 5.18 (q, J = 7.0 Hz); SEC (THF relative to PS standards) M_n: 30.7 kDa, M_w: 40.7 kDa, Đ: 1.3; T_g: 50 ^{o}C.

2.4%L$_{err}$. **Bn-LG** (1.7 g, 7.0 mol), **Bn-LLG** (0.06 g, 0.18 mol) and 10% Pd/C (0.09 g, 5% w/w) were combined in dry EtOAc (70 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (1.0 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ LG: 5.24 (q, J = 7.2 Hz, 1H), 4.29 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.0 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H), LLG: 5.22 (q, J = 7.2 Hz).

2.4% errormer (ratio 1:40.7 LLG:LG). **LG** (1.0 g, 6.73 mmol), **LLG** (0.04 g, 0.17 mmol), and DPTS (0.27 g, 0.91 mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.3 ml) with stirring at RT under N_2. DIC (1.6 ml, 10.4 mmol) was added dropwise and the reaction was allowed to stir for 3h. The polymerization mixture was dissolved in a minimum amount of

CH_2Cl_2 and precipitated into MeOH (75 ml). The solid was redissolved and then precipitated in MeOH (75 ml) and dried under vacuum to yield a colorless solid (0.51 g, 56 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ Poly LG: 5.23 (q, J = 7.0 Hz, 1H), 4.86 (d, J = 15.6 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 1.62 (d, J = 7.2 Hz, 3H), LLG Errors: 5.19 q, J = 7.0 Hz); SEC (THF relative to PS standards) M_n: 17.2 kDa, M_w: 28.0 kDa, Đ: 1.6; T_g: 45 °C.

5.0%L$_{err}$. **Bn-LG** (1.7 g, 7.0 mol), **Bn-LLG** (0.12 g, 0.39 mol) and 10% Pd/C (0.09 g, 5% w/w) were combined in dry EtOAc (75 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (1.1 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ LG: 5.24 (q, J = 7.0 Hz, 1H), 4.29 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.5 Hz, 1H), 1.56 (d, J = 7.0 Hz, 3H), LLG: 5.19 (q, J = 7.0 Hz), 4.29 (d, J = 21.0 Hz).

5.0% errormer (ratio 1:19 LLG:LG). **LG** (1.01 g, 6.8 mmol), **LLG** (0.082 g, 0.37 mmol), and DPTS (0.29 g, 0.99 mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.4 ml) with stirring at RT under N_2. DIC (1.7 ml, 10.8 mmol) was added dropwise and the reaction was allowed to stir for 3h. The polymerization mixture was dissolved in a minimum amount of CH_2Cl_2 and precipitated into MeOH (300 ml). The solid was redissolved and then precipitated in MeOH (250 ml) and dried under vacuum to yield a colorless solid (0.55 g, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ Poly LG: 5.23 (q, J = 7.0 Hz, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz,) 1.57 (d, J = 7.2 Hz, 3H), LLG Errors: 5.19 (q, J = 7.0 Hz), 4.62 (d, J = 16.2 Hz), SEC (THF relative to PS standards) M_n: 21.5 kDa, M_w: 31.7 kDa, Đ: 1.5; T_g: 49 °C.

8.4%L$_{err}$. Bn-LG (1.7 g, 7.0 mol), **Bn-LLG** (0.22 g, 0.70 mol) and 10% Pd/C (0.10 g, 5% w/w) were combined in dry EtOAc (80 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (1.2 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ LG: 5.22 (q, J = 7.2 Hz, 1H), 4.29 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.0 Hz, 1H), 1.56 (d, J = 7.0 Hz, 3H), LLG: 5.23 (q, J = 7.2 Hz), 5.18 (q, J = 7.0 Hz, 1H), 4.29 (d, J = 17.5 Hz).

8.4% errormer (ratio 1:10.9 LLG:LG). **LG** (0.99 g, 6.7 mmol), **LLG** (0.15 g, 0.88 mmol), and DPTS (0.29 g, 0.97 mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.45 ml) with stirring at RT under N_2. DIC (1.7 ml, 11.1 mmol) was added dropwise and the reaction was allowed to stir for 3 h. The polymerization mixture was dissolved in a minimum amount of CH_2Cl_2 and precipitated into MeOH (300 ml). The solid was redissolved and then precipitated in MeOH (250 ml) and dried under vacuum to yield a colorless solid (0.40 g, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ Poly LG: 5.23 (q, J = 7.2 Hz, 1H), 4.86, (d, J = 16.2 Hz, 1H), 4.63 (d, J = 15.6 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H), LLG Errors: 5.18 (q, J = 7.2 Hz), 4.62 (d, J = 15.6 Hz); SEC (THF relative to PS standards) M_n: 14.0 kDa, M_w: 22.4 kDa, Đ: 1.6; T_g: 48 ^{o}C.

11.6%L$_{err}$. Bn-LG (1.7 g, 7.0 mol), **Bn-LLG** (0.33 g, 1.0 mol) and 10% Pd/C (0.11 g, 5% w/w) were combined in dry EtOAc (80 mL) under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm of H_2. The reaction mixture was filtered over celite, EtOAc reduced in volume under reduced pressure, dried over $MgSO_4$, filtered over celite, and concentrated *in vacuo* to provide the product as a colorless liquid (1.3 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ LG: 5.21 (q, J = 7.2 Hz, 1H), 4.29

(d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.5 Hz, 1H), 1.55 (d, J = 7.5 Hz, 3H), LLG: 5.23 (q, J = 7.0 Hz), 5.18 (q, J = 7.2 Hz), 4.29 (d, J = 17.5 Hz), 1.56 (d, J = 7.0 Hz).

11.6% errormer (ratio 1:7.6 LLG:LG). **LG** (1.02 g, 6.9 mmol), **LLG** (0.23 g, 1.0 mmol), and DPTS (0.31 g, mmol) were combined in dry CH_2Cl_2 (3 M with respect to substrate, 2.6 ml) with stirring at RT under N_2. DIC (1.85 ml, 12 mmol) was added dropwise and the reaction was allowed to stir for 3 h. The polymerization mixture was dissolved in a minimum amount of CH_2Cl_2 and precipitated into MeOH (300 ml). The solid was redissolved and then precipitated in MeOH (250 ml) and dried under vacuum to yield a colorless solid (0.67 g, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ Poly LG: 5.23 (q, J = 7.0 Hz, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H), LLG Errors: 5.18 (q, J = 7.2 Hz), 4.85 (d, J = 16.2 Hz), 4.62 (d, J = 15.6 Hz); SEC (THF relative to PS standards) M_n: 18.5 kDa, M_w: 29.0 kDa, Đ: 1.6; T_g: 48 ^{o}C.

3.4.4 Reactivity of monomers study.

Bn-LLG (50 mg, 0.16 mmol, 1 equiv.) was combined with **LLG-Si** (44 mg, 0.096 mmol, 0.62 equiv.), **LG-Si** (37.2 mg, 0.096 mmol, 0.58 equiv.), DPTS (9.5 mg, 0.032 mmol, 0.2 equiv.) and DCC (36.5 mg, 0.18 mmol, 1.1 equiv.) in 1.6 mL of dry CH_2Cl_2 under N_2. The reaction mixture was stirred overnight at RT. The crude product mixture was filtered to remove dicyclohexylurea, concentrated *in vacuo*. The crude product mixture was a colorless oil (118 mg, 98%).

4.0 SEQUENCE-CONTROLLED COPOLYMERS PREPARED VIA ENTROPY-DRIVEN RING-OPENING METATHESIS POLYMERIZATION

Sections 4.1 – 4.4 of this chapter have been reprinted with permission from Weiss, R. M.; Short, A. L.; Meyer, T. Y. "Sequence-Controlled Copolymers Prepared via Entropy-Driven Ring-Opening Metathesis Polymerization" *ACS Macro Letters* **2015**, *4*, 1039. Copyright 2015 American Chemical Society.[21]

4.1 INTRODUCTION

4.1.1 Recent advances in sequenced copolymers

The sophisticated interplay between structure and function has long been apparent in naturally occurring biological architectures. In these systems, a precisely sequenced framework prepared from a small pool of simple monomers imparts the properties responsible for the characteristic functions. The important relationship between sequence and properties would be expected to translate to synthetic polymers but has been less studied. Efforts in non-biological polymers have historically focused on the more easily attainable and less sequence-controlled copolymer variants, i.e., random, alternating, block, and gradient structures.[48,66,150,151] Recent advances have expanded the availability of more complex microstructures and the concomitant studies of these

new materials have established the potential for sequenced-based property control.[8,43,51,53,73,104,117,152-162]

4.1.2 Segmer assembly polymerization of PLGAs

We have long been interested in understanding the influence of sequence on polymer properties[10-12,15-20,163] and have focused significant attention on poly(lactic-*co*-glycolic acids) (PLGAs) and other α-hydroxy acid macromolecules due to their importance as non-toxic biodegradable bioengineering materials.[24,26,30] Our early efforts to prepare these materials relied on a segmer assembly polymerization (SAP) approach. Using this method, we prepared a library of sequenced copolymers and found that the rate of degradation and release of guest molecules is sequence-dependent.[10,15,163] Although these results were exciting and established the power of sequence in tuning properties, the full realization of the potential of these materials was limited by the lack of molecular weight control inherent in the step-growth SAP methodology. We, therefore, set out to develop a method to obtain sequence-controlled polymers with improved control of chain length without sacrificing the fundamental poly(alkylester) structure.

4.1.3 Entropy-driven ring-opening metathesis polymerization

Herein, we report a strategy for making sequenced copolymers that utilizes entropy-driven ring-opening metathesis polymerization (ED-ROMP) and produces polymers with controlled molecular weights. ED-ROMP involves the ring-opening of a low-strain or unstrained cyclic olefin to produce an entropically favored polymer.[67,68,164,165]

There are several characteristics of ED-ROMP which make this an ideal approach to the problem of sequenced copolymers: sequence conservation, generality and inherent molecular weight control. As with all ROMP reactions, the metathesis is highly selective and atom connectivity within the ring remains unchanged. Hillmyer and coworkers have cleverly exploited these characteristics to create sequenced copolymers from the ROMP of variously substituted cyclooctene rings.[104] Although this process resembles ED-ROMP in some aspects, the reaction is inherently limited to rings that exhibit ring strain.

Also related to the current work is the recent report by Hawker and coworkers in which a macrocyclic monomer with embedded sequence was polymerized using a novel relay ring-opening mechanism. In this system, which does not rely on ED-ROMP driving forces, a specialized trigger moiety was employed and is retained in the resulting polymer.[105]

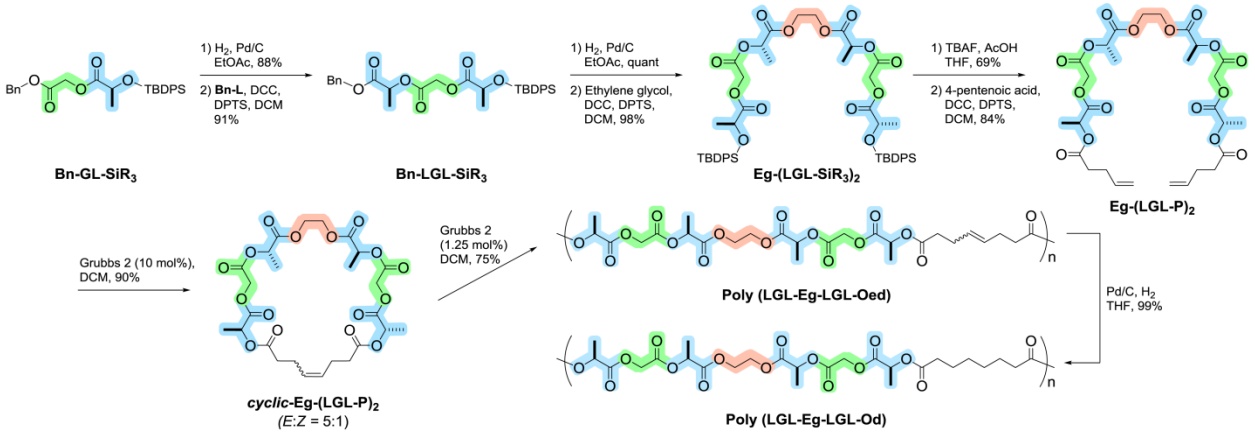
Entropy is the primary driving force for the ED-ROMP reactions utilized in the current study. Concentration is used to favor chains over rings under conditions which allow for equilibration. Molecular weight control is possible because the number of chains is determined by the catalyst introduced. Final molecular weight is then a function of monomer-to-initiator ratio and the concentration, which determines the ring-chain equilibrium. The intrinsic molecular weight control differentiates ED-ROMP from the closely related, primarily step-growth acyclic diene metathesis polymerization (ADMET).[53,166,167]

ED-ROMP and the more general entropy driven ring-opening polymerization (ED-ROP) have been applied previously to a variety of macrocycles[168-170] and the mechanism is well understood. To the best of our knowledge, this is the first example of ED-ROMP being explicitly used to produce polymers that display within them a series of sequenced monomers.

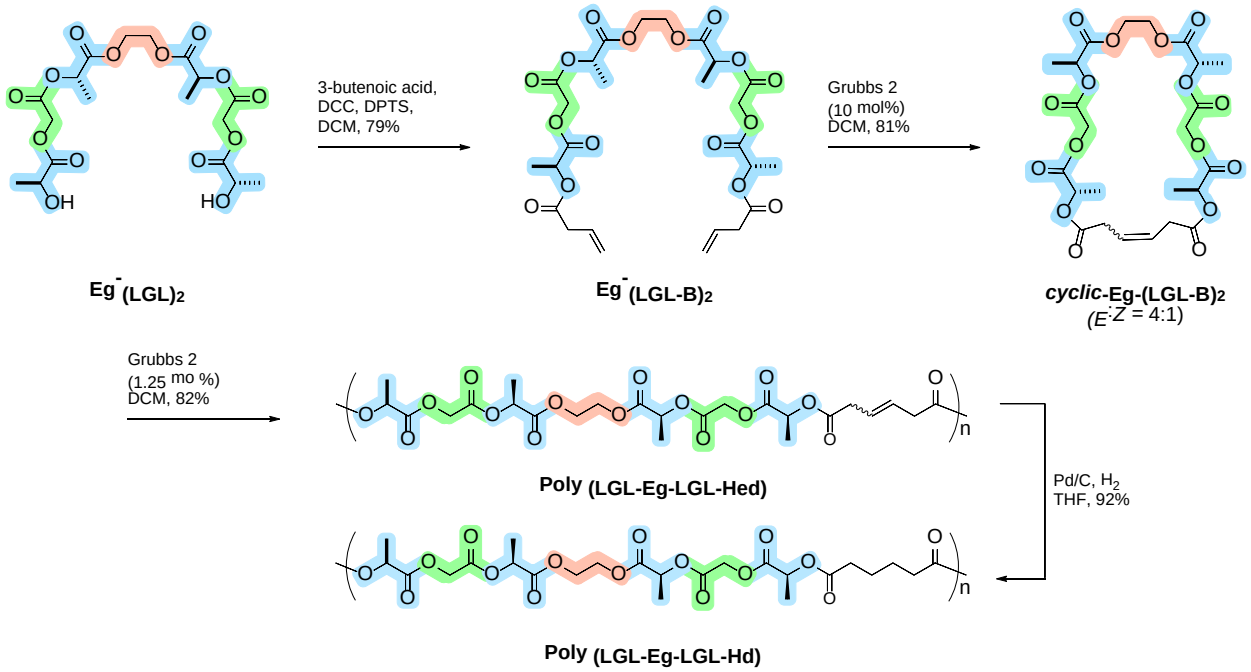
4.2 RESULTS AND DISCUSSION

4.2.1 Synthesis of sequenced macrocycles and subsequent ED-ROMP

We began our investigation by first preparing cyclic precursors containing L-lactic acid (**L**), glycolic acid (**G**), and ε-caprolactone (**C**)-derived sequenced oligomers (segmers).[15-17] A typical synthesis begins with the doubly protected subunit **Bn-GL-SiR$_3$** (**Scheme 8**). Following hydrogenolysis to remove the benzyl group, carbodiimide-promoted coupling of **GL-SiR$_3$** with **Bn-L** produced the trimer **Bn-LGL-SiR$_3$**. Deprotection of the acid followed by coupling to ethylene glycol (**Eg**) yielded the palindromic segmer **Eg-(LGL-SiR$_3$)$_2$**. Removal of the silyl protecting group with TBAF/AcOH gave the fully deprotected diol **Eg-(LGL)$_2$**, which was coupled to either 4-pentenoic acid (**P**) or 3-butenoic acid (**B**, **Scheme 9**) to produce a diolefin-terminated segmer. This convergent synthetic approach allows for the facile assembly of segmers of any length and sequence from a common set of building blocks using standardized procedures. Optimized approaches could be easily substituted if a particular sequence was targeted for scale up.

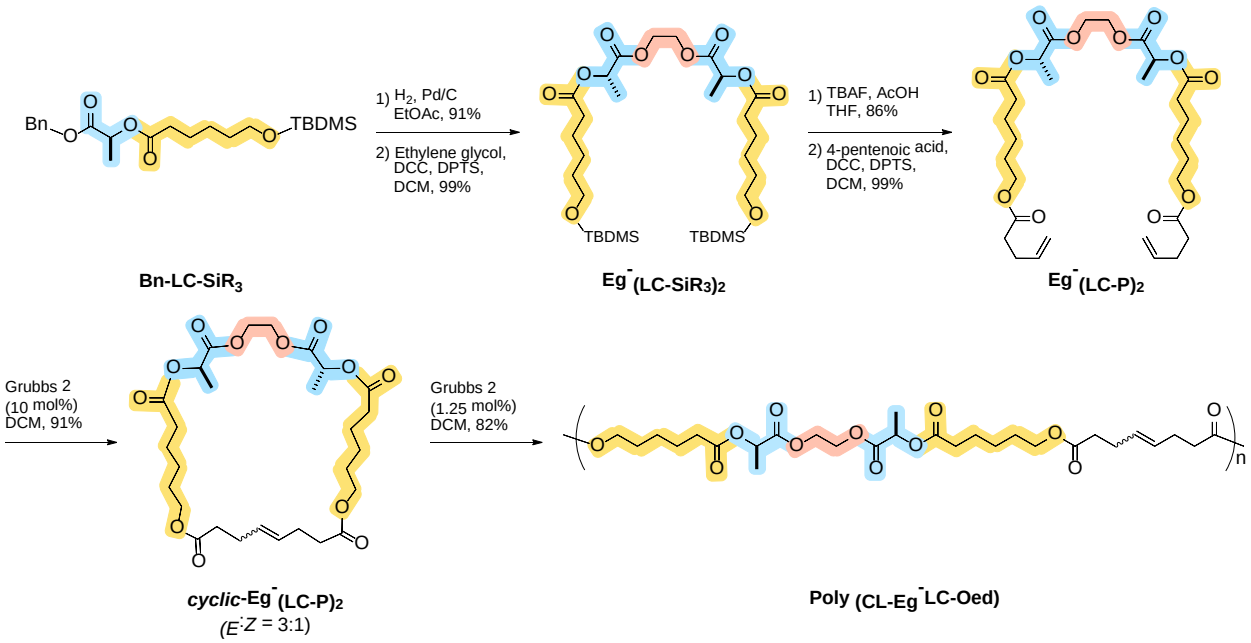


Scheme 8. Synthesis of sequenced copolymer **Poly (LGL-Eg-LGL-Od)**.

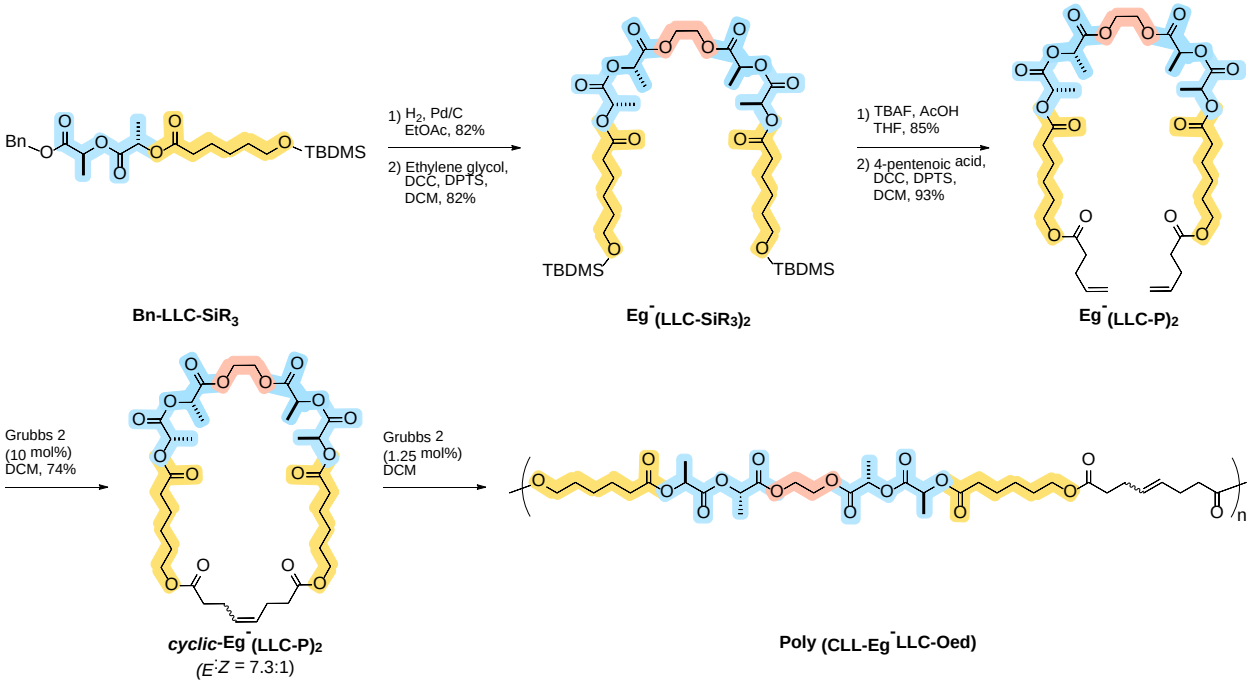


Scheme 9. Synthesis of sequenced copolymer **poly (LGL-Eg-LGL-Hd)**

Ring-closing metathesis (RCM)[171-173] with Grubbs' 2nd generation catalyst (Grubbs 2) yielded the desired cyclic macromonomers. An analogous route was employed to prepare ***cyclic*-Eg-(LC-P)$_2$** and ***cyclic*-Eg-(LLC-P)$_2$ (Scheme 10** and **Scheme 11**, respectively**)**. Although dilute conditions were used to inhibit oligomerization, the reaction was easily performed on a 2-3 g scale.



Scheme 10. Synthesis of sequenced copolymer **poly (CL-Eg-LC-Oed)**



Scheme 11. Synthesis of sequenced copolymer **poly (CLL-Eg-LLC-Oed)**

Once the requisite macrocycles had been constructed, ED-ROMP was carried out in the presence of Grubbs 2 (**Scheme 8**). To promote polymerization over nonproductive intramolecular ring formation, the reactions were conducted at high concentration (0.7 M). The polymerizations were quenched with ethyl vinyl ether to provide a series of polymers whose

physical properties are shown in **Table 7**. The M_ns of the polymers ranged from 26 to 60 kDa. The T_gs of the polymers depended on both sequence and spacer composition, ranging from -11 ^oC for the **LLC** polymer to 32 ^oC for the **LGL** polymer with **Hed** spacer (**Figure 20** and **Figure 21**). Interestingly, the T_gs of the two **poly (CL-Eg-LC-Oed)** samples were both -27 ^oC, despite a significant difference in molecular weight (**Figure 21**). Therefore, both polymers are in the regime where thermal properties are no longer affected by degree of polymerization. The SAP approach, which generally produced polymers of lower molecular weights, exhibited a range of T_gs for similar sequences.[15-17]

Table 7. Polymer molecular weight and thermal data

Polymer	M/cat	T_g (^oC)[a]	M_n (kDa)	M_w (kDa)	Đ
Poly (CL-Eg-LC-Oed)-1	78	-27	26[b]	32[b]	1.3[b]
Poly (CL-Eg-LC-Oed)-2	164	-27	39[b]	48[b]	1.3[b]
Poly (CLL-Eg-LLC-Oed)-1	20	-	24[c]	32[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-2	19	-	29[c]	37[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-3	45	-	42[c]	53[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-4	45	-11	47[c]	60[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-5	75	-	48[c]	63[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-6	75	-	50[c]	65[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-7	125	-	60[c]	78[c]	1.3[c]
Poly (CLL-Eg-LLC-Oed)-8	126	-	56[c]	71[c]	1.3[c]
Poly (LGL-Eg-LGL-Oed)	78	18	33[b]	44[b]	1.3[b]
Poly (LGL-Eg-LGL-Od)[d]	na	13	28[b]	41[b]	1.5[b]
Poly (LGL-Eg-LGL-Hed)	80	32	33[b]	46[b]	1.4[b]
Poly (LGL-Eg-LGL-Hd)[d]	na	23	27[b]	42[b]	1.5[b]

a) First heating cycle at 10 ^oC/min; b) SEC in THF, relative to PS standards; c) SEC in THF, absolute molecular weight data; d) produced by hydrogenation of the corresponding Oed or Hed precursor.

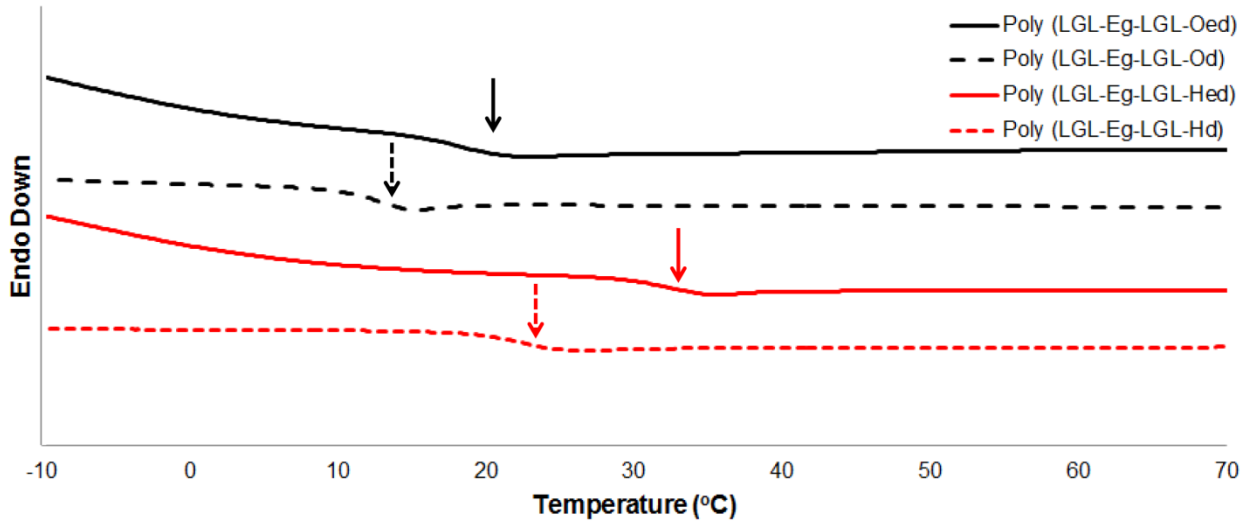


Figure 20. DSC thermogram of **poly (LGL-Eg-LGL-Oed)**, **poly (LGL-Eg-LGL-Od)**, **poly (LGL-Eg-LGL-Hed)**, and **poly (LGL-Eg-LGL-Hd)**. Arrows denote the T_g of each sequenced copolymer.

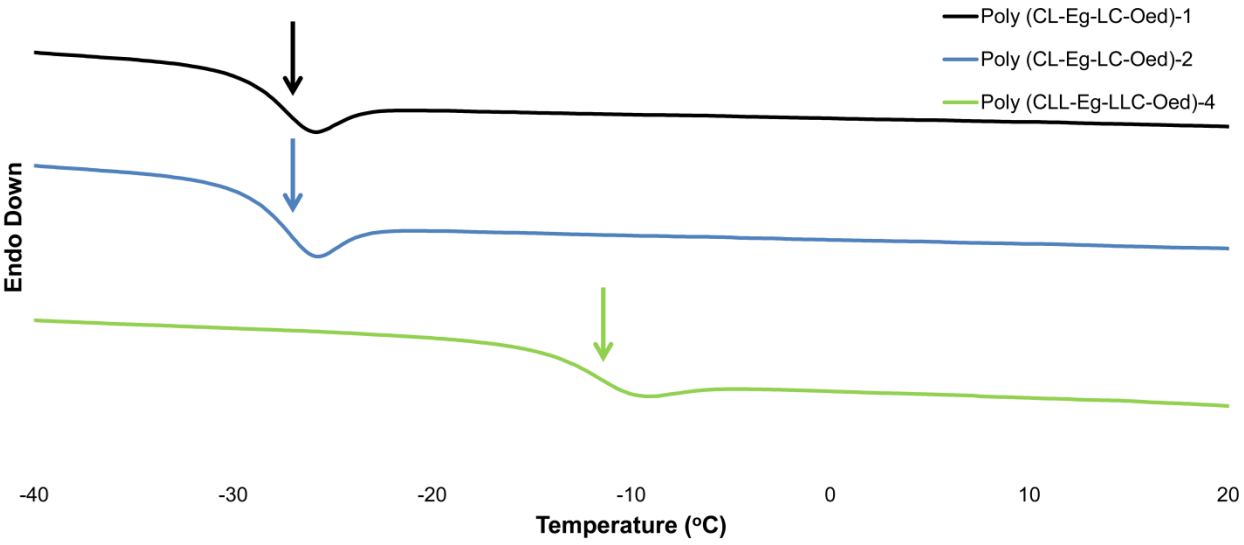


Figure 21. DSC thermogram of **poly (CL-Eg-LC-Oed)-1**, **poly (CL-Eg-LC-Oed)-2**, and **poly (CLL-Eg-LLC-Oed).** Arrows denote the T_g of each sequenced copolymer.

4.2.2 ^{1}H NMR spectroscopy characterization of synthesized copolymers

Based on our extensive experience characterizing SAP-produced α-hydroxy acid polymers with varying sequences[15-17] we can confirm conclusively that the sequences embedded in the macrocycles were retained during the polymerization process (**Figure 22-Figure** 27). Using ^{1}H

NMR spectroscopy, which we have previously shown is extremely sensitive to sequence in this class of polymers, we can rule out scrambling and epimerization.

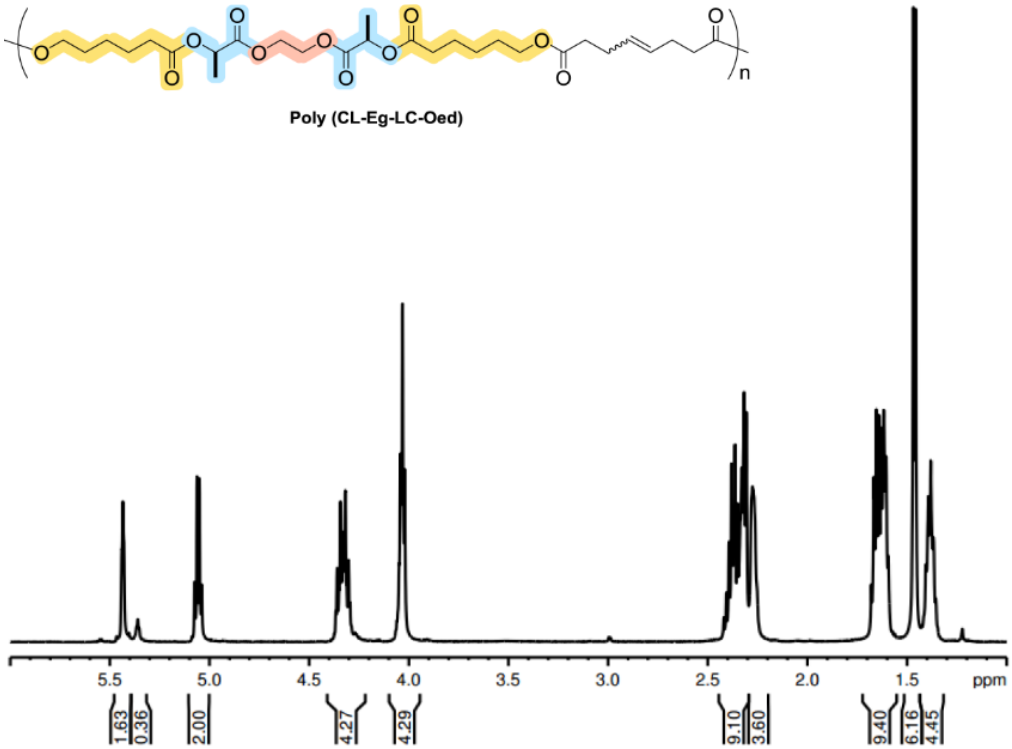


Figure 22. ^{1}H NMR (600 MHz) spectrum of **poly (CL-Eg-LC-Oed)**

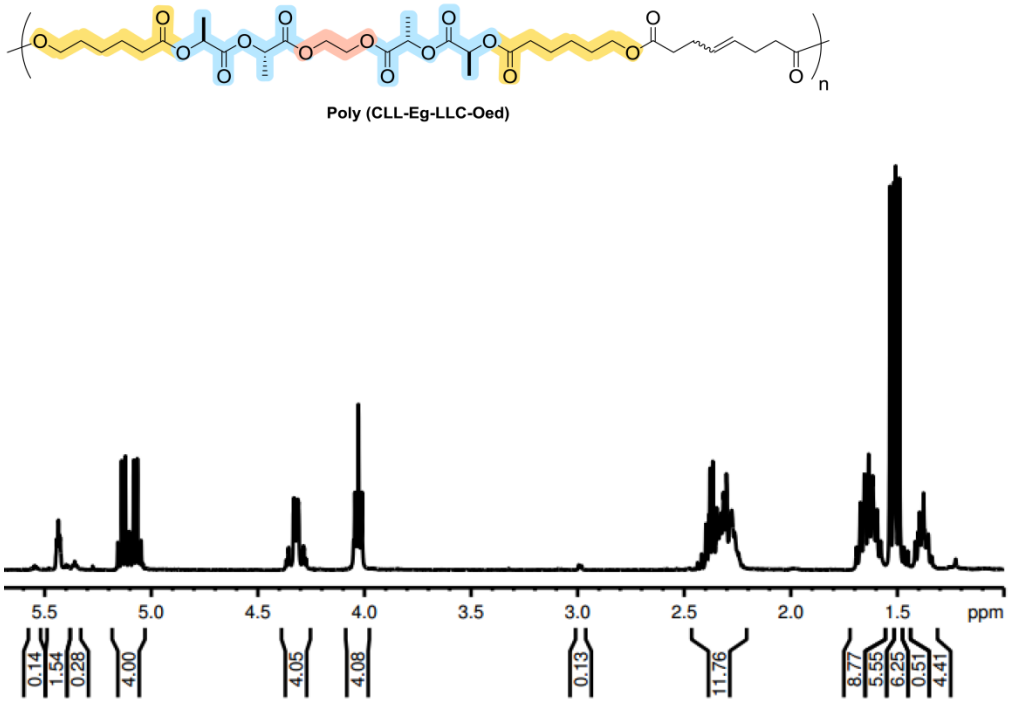


Figure 23. ^{1}H NMR (400 MHz) spectrum of **poly (CLL-Eg-LLC-Oed)-4**

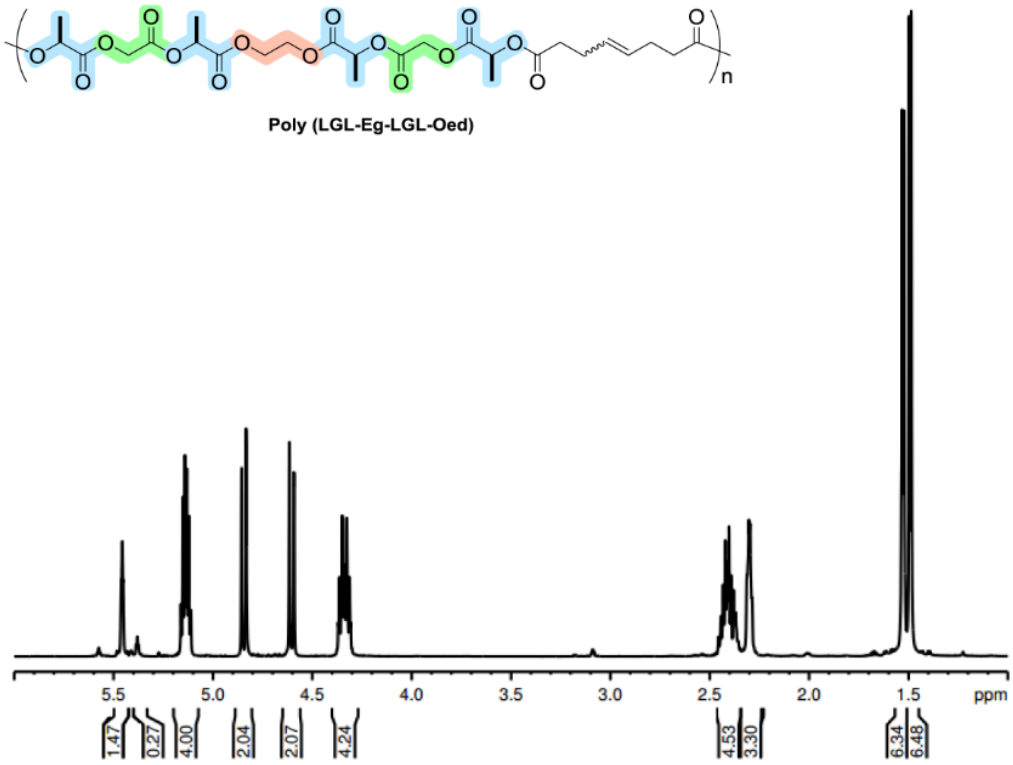


Figure 24. ^{1}H NMR (700 MHz) spectrum of **poly (LGL-Eg-LGL-Oed)**

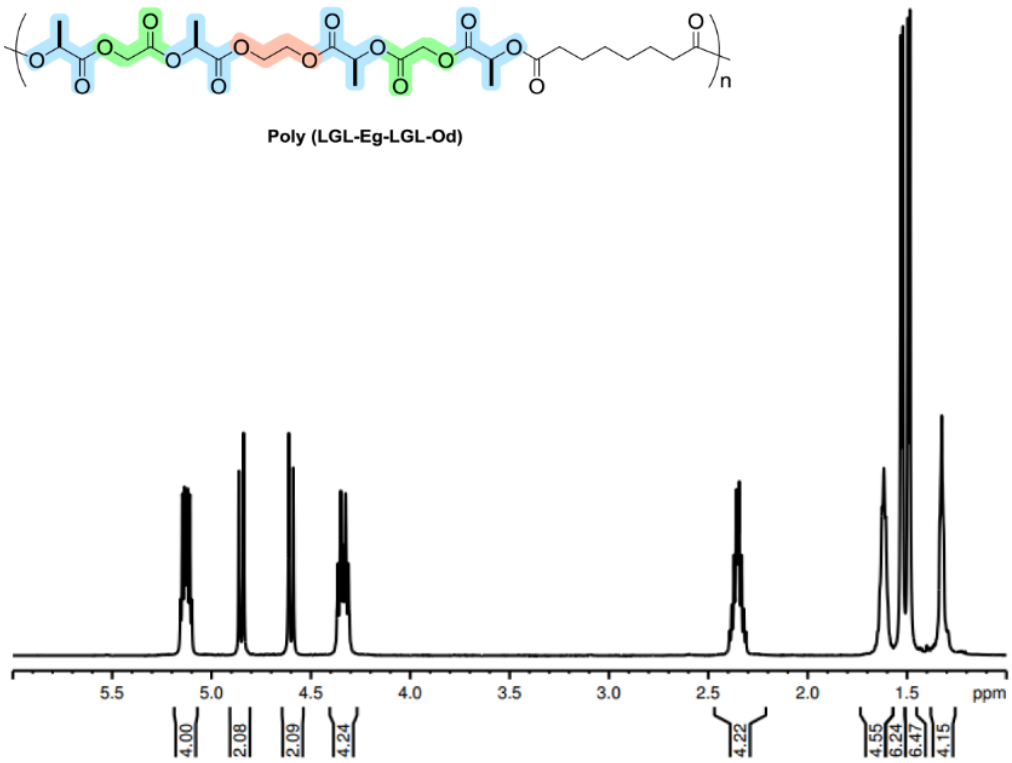


Figure 25. ^{1}H NMR (700 MHz) spectrum of **poly (LGL-Eg-LGL-Od)**

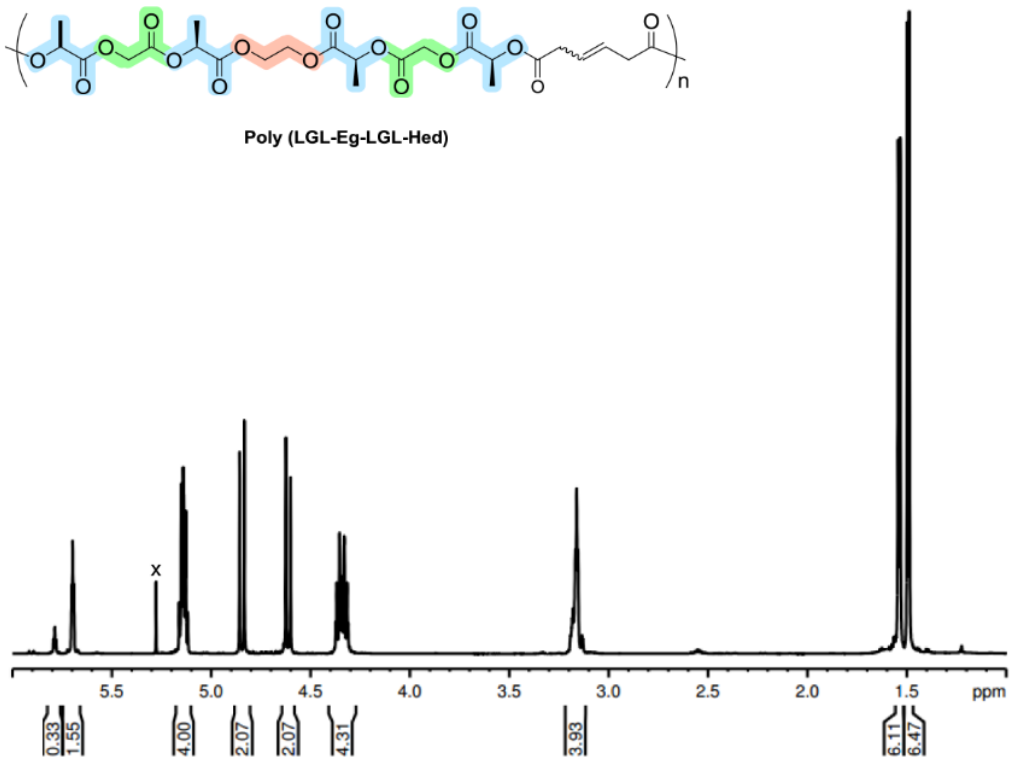


Figure 26. ^{1}H NMR (700 MHz) spectrum of **poly (LGL-Eg-LGL-Hed)**

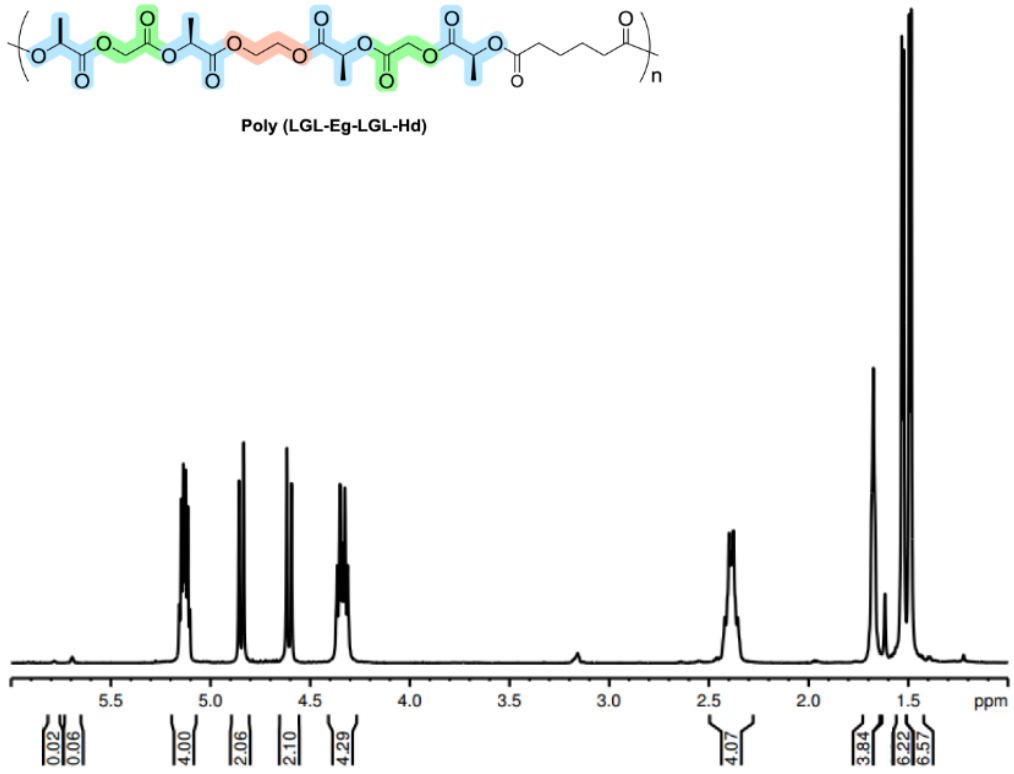


Figure 27. ^{1}H NMR (700 MHz) spectrum of **poly (LGL-Eg-LGL-Hd)**

4.2.3 ED-ROMP polymerization kinetic study

To determine if these reactions conform to the expectations of an ED-ROMP process, kinetic studies of ***cyclic*-Eg-(LGL-P)$_2$** polymerizations were carried out by quenching aliquots at specific time intervals. SEC characterization of these aliquots confirmed that the M_n sharply increased at the onset of propagation and reached a maximum within 15 min (**Figure 28a**, **Table 8**). As expected during ED-ROMP, the M_n decreased and the dispersity (Đ) increased as secondary metathesis reactions became more prevalent. Secondary metathesis in this case means reaction of the catalytically active metal center with an internal double bond in the polymer chain. Secondary metathesis leads to ring-chain equilibration but does not scramble the embedded sequence.

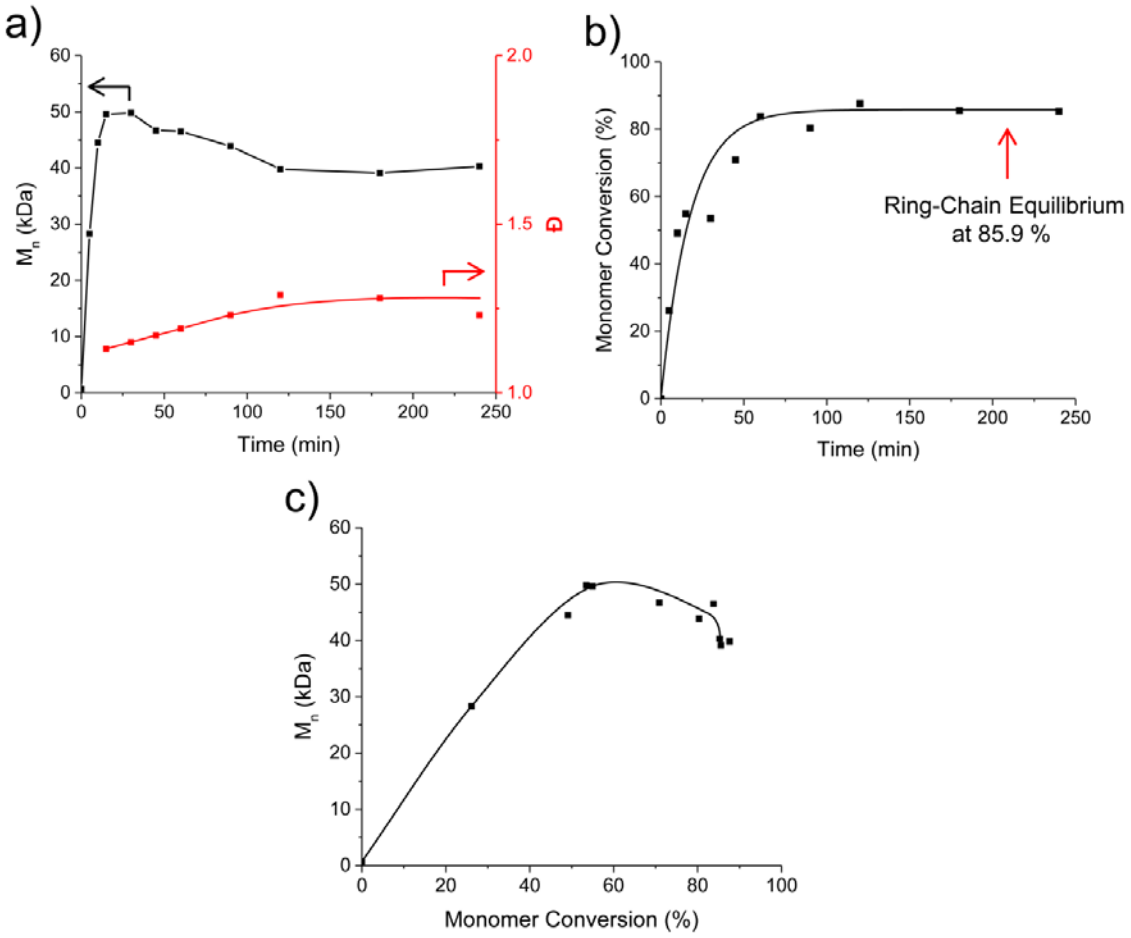


Figure 28. ED-ROMP of ***cyclic*-Eg-(LGL-P)$_2$** a) M_n vs time (black) and dispersity vs time (red); b) monomer conversion (%) vs time; c) M_n vs monomer conversion (%).

Table 8. Poly (LGL-Eg-LGL-Oed) polymerization kinetics data

Reaction	Reaction Time (min)	Mass Monomer (g)	Catalyst mass (mg)	Solvent Amount (mL)	Percent Conversion (%)[d]	DP[e]	M_n (kDa)[f]	M_w (kDa)[f]	Đ[f]
1[a]	5	0.2101	3.7	0.50	26.1	49	28.3	38.7	1.37
2[a]	10	0.2136	3.7	0.50	49.1	77	44.5	52.7	1.18
3[a]	15	0.2043	3.6	0.49	54.9	86	49.6	56.1	1.13
4[a]	30	0.2158	3.8	0.51	53.4	87	49.8	57.2	1.15
5[a]	45	0.2157	3.8	0.51	70.7	81	46.7	54.6	1.17
6[b]	60	0.2107	3.7	0.50	83.8	81	46.5	55.3	1.19
7[c]	90	0.2123	3.7	0.50	80.4	76	43.9	53.9	1.23
8[b]	120	---	---	---	87.6	69	39.8	51.3	1.29
9[c]	180	---	---	---	84.9	68	39.1	50.2	1.28
10[b]	240	---	---	---	85.9	70	40.3	49.7	1.23

This table contains data compiled from three sets of kinetics experiments (a-c) carried out under similar conditions. a) Separate vials containing reaction mixtures were prepared parallel to one another and quenched at the appropriate time; b) and c) aliquots were removed from a single reaction vessel and quenched at the appropriate time; d) obtained by integration of the glycolic methylene region of the ^{1}H NMR spectra e) Calculated from the obtained M_n values; f) SEC in THF, relative to polystyrene standards.

Monomer conversion rose rapidly and then saturated at a level determined by ring-chain equilibrium, in this case 85.9% (**Figure 28b**). Conversion was monitored using ^{1}H NMR spectroscopy. The chemical shifts of the diastereotopic methylene protons of **G**, found at 4.9-4.55 ppm, were distinct for the ring-closed and ring-opened species (**Figure 29**, **Figure 30**). The effects of secondary metathesis are also well illustrated by the plot of molecular weight vs. conversion (**Figure 28c**).

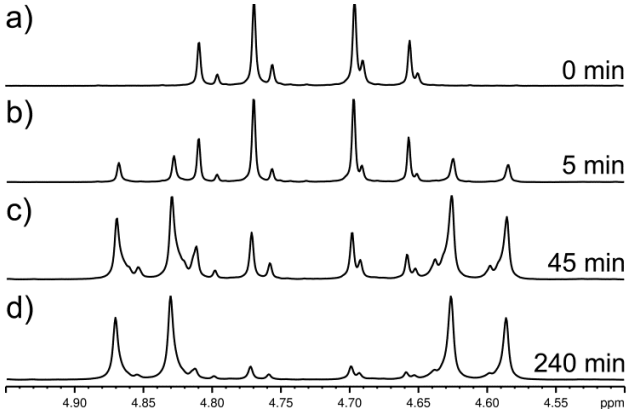


Figure 29. The 400 MHz ^{1}H NMR spectra of ED-ROMP of ***cyclic*-Eg-(LGL-P)$_2$** to poly **(LGL-Eg-LGL-Oed)**. Major resonances from *trans* isomers and minor resonances from *cis* isomers.

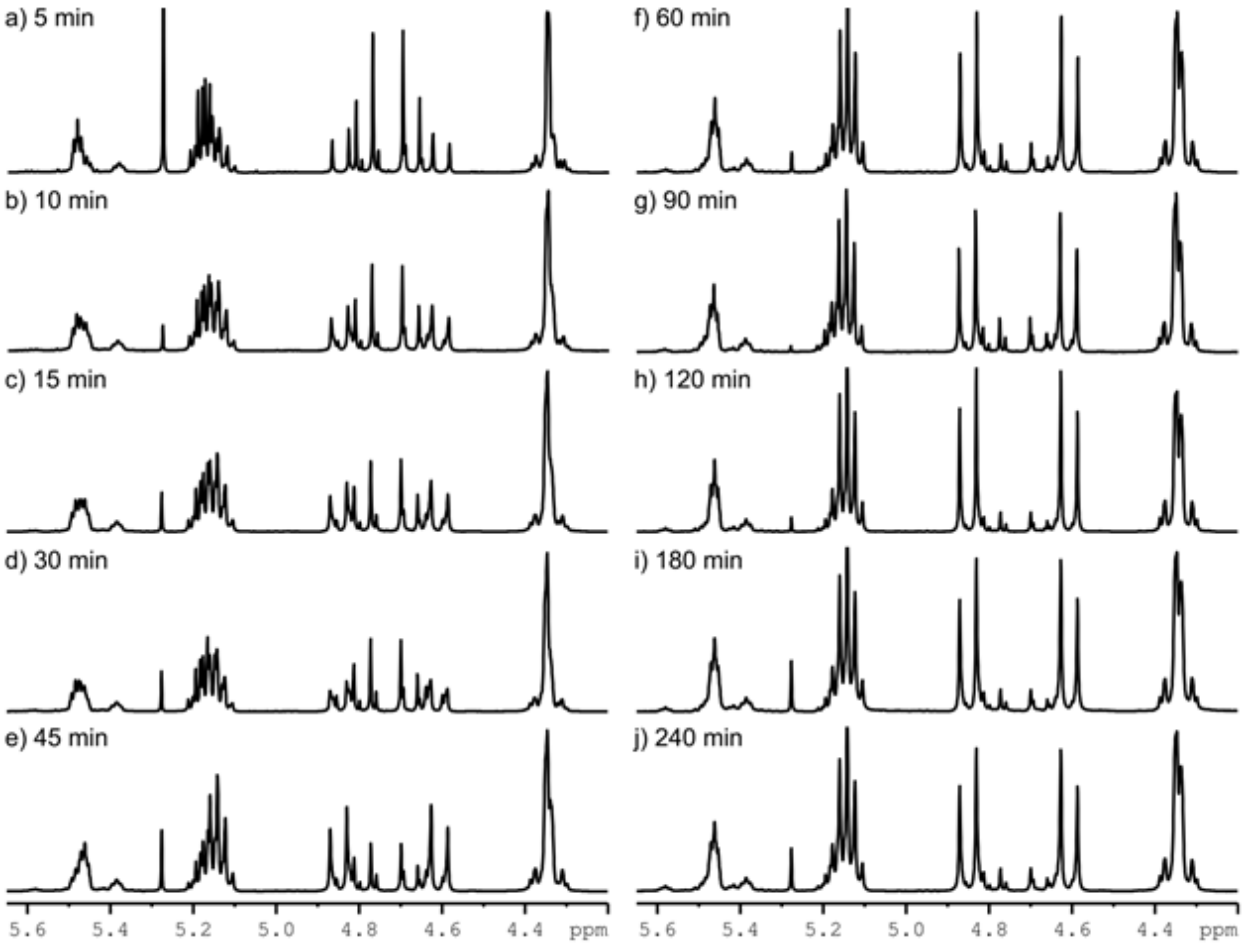


Figure 30. The 400 MHz ^{1}H NMR spectra (5.65-4.2 ppm) at varying time points of **poly (LGL-Eg-LGL-Oed)** synthesized from ***cyclic*-Eg-(LGL-P)$_2$** by ED-ROMP.

The initial linear phase was followed by a gradual drop in molecular weight at moderate conversions. Once the ring-chain equilibrium was reached the molecular weight continued to decrease due to secondary metathesis reactions. The dispersities gradually rose to 1.3. Importantly, we see evidence in these initial experiments for the desired molecular weight control. It is clear from the kinetic studies that the reaction is following the course expected for an ED-ROMP process. As such, molecular weight is governed by the monomer-to-catalyst ratio ([M]/[cat]) and the concentration of the reaction, which determine the proportion of monomers in chains with catalyst end groups.[164,174] Consistent with this expectation, we found that when the

[M]/[cat] ratio was adjusted from 78:1 to 164:1 in the ED-ROMP of ***cyclic*-Eg-(LC-P)$_2$**, the M_n of the crude reaction mixture increased from 26 to 39 kDa (Table 7).

In a more detailed study of molecular weight control a series of polymerizations of ***cyclic*-Eg-(LLC-P)$_2$** were carried out (**Table 7**, **Scheme 11** and **Table 9**). Four different [M]/[cat] ratios (20, 45, 75, and 125) were used in duplicate polymerizations and their absolute molecular weights were determined (**Figure 31**). Importantly, the M_ns increased consistently as a function of the [M]/[cat] ratio, although they did not track perfectly with those theoretically predicted. The pattern of the deviation, where molecular weights start higher than expected for low [M]/[cat] ratios and gradually decrease to lower than expected as the ratio of monomer to catalyst increases, has been observed previously for ED-ROMP polymerizations.[175] It is also important to note that the reactions were highly reproducible—duplicate conditions produced nearly identical molecular weights. Note: as the ring-chain equilibrium could not be calculated for this monomer because of an unfortunate overlap of NMR signals, the previously observed ratio of 85.9% was used to estimate the predicted values in **Figure 31**. Molecular weight predictions based on a reasonable range of ratios (80-90%) do not substantially change the analysis (**Figure 32**).

Table 9. Poly (CLL-Eg-LLC-Oed) molecular weight control study data

Poly	monomer (mg)	Monomer (mol)	Cat (mol)	Mol % cat	CH_2Cl_2 (µL)	[M]/[cat]	Adjusted theoretical M_n (kDa)[a]	M_n (kDa)[b]	M_w (kDa)[b]	Đ[b]
1	50.9	$6.66x10^{-5}$	$3.39x10^{-6}$	5.10	95	20	12.0	24.2	31.8	1.31
2	50.5	$6.62x10^{-5}$	$3.39x10^{-6}$	5.14	94	19	12.0	28.9	37.3	1.29
3	48.1	$6.73x10^{-5}$	$1.49x10^{-6}$	2.21	96	45	27.8	41.8	52.8	1.27
4	48.1	$6.73x10^{-5}$	$1.49x10^{-6}$	2.21	96	45	27.8	47.4	59.6	1.26
5	47.7	$6.67x10^{-5}$	$8.92x10^{-7}$	1.34	95	75	45.9	48.4	63.0	1.30
6	48.0	$6.71x10^{-5}$	$8.92x10^{-7}$	1.33	96	75	46.2	50.4	65.3	1.30
7	48.0	$6.73x10^{-5}$	$5.35x10^{-7}$	0.80	96	125	77.0	59.5	78.2	1.31
8	95.2	$1.33x10^{-4}$	$1.06x10^{-6}$	0.80	190	126	76.7	56.1	71.6	1.28

This table contains data compiled from four sets of molecular weight control experiments carried out under similar conditions. The mol % catalyst was varied between each set. a) This value was calculated by applying a ring-chain equilibrium correction factor obtained from the kinetics experiment. The [M]/[cat] value was multiplied by 0.859 and then converted to M_n. These values were used in Figure 4 for the theoretical living polymerization values; b) SEC in THF, actual molecular weight data.

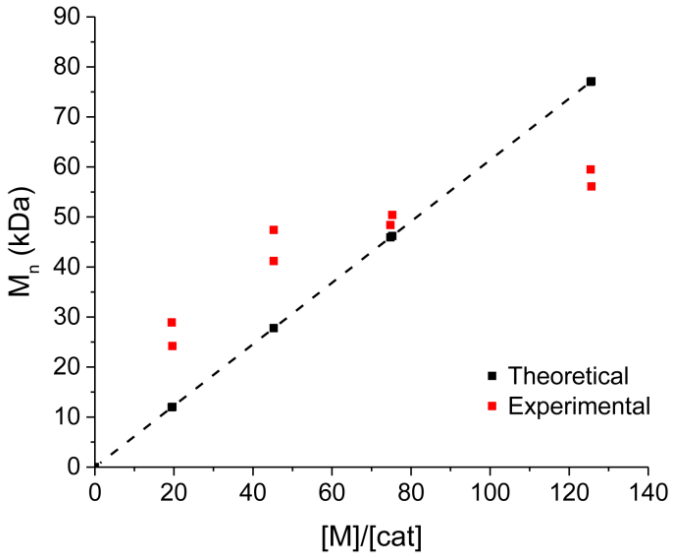


Figure 31. Molecular weight control study of the polymerization of ***cyclic*-Eg-(LLC-P)$_2$** to form **poly (CLL-Eg-LLC-Oed)** using varying [M]/[cat] ratios. The molecular weights determined are in red, while the dotted black line represents a theoretical living polymerization taking ring-chain equilibrium into account.

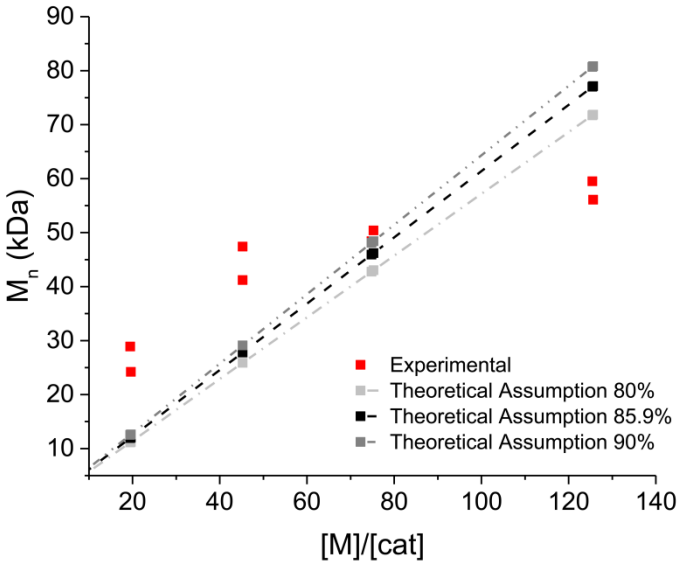


Figure 32. Molecular weight control study of the polymerization of *cyclic*-Eg-(LLC-P)$_2$ to form **poly (CLL-Eg-LLC-Oed)** using varying [M]/[cat] ratios (20, 45, 75, and 125). The molecular weights determined experimentally are in red. The dotted lines represent theoretical living polymerizations taking three different ring-chain equilibria assumptions into account (80%, 85.9%, and 90%). The polymerizations in this study had the same monomer to solvent concentration as the kinetics study (**Figure 28** and **Figure 29**, **Table 8**). Since concentration determines the ring-chain equilibrium and the concentration was the same as the kinetics study, we chose to use 85.9% to calculate the theoretical living polymerization values. It can be seen that changing to either 80% or 90% doesn't change the overall trend of either being above or below the theoretical M_n.

4.2.4 Copolymer thermal properties

The olefinic group in the metathesis "linker" could be removed by hydrogenation. The saturated polymers containing the LGL sequence were isolated as colorless solids with no visual evidence of catalyst contamination and conversions >97% (**Scheme 8** and **Scheme 9**). Hydrogenation decreased the T_g of these polymers by 4–10 ^oC.

4.3 CONCLUSIONS

In summary, cyclic macromonomers containing ring-opened ε-caprolactone, lactic and glycolic acids were prepared by RCM and subsequently polymerized by ED-ROMP to yield sequence-preserved copolymers with molecular weight control. Kinetic studies confirmed the adherence of the reaction to the expected ED-ROMP pathway and the extension of the procedure to multiple sequences established that the polymerization conditions are sequence-independent.

The ED-ROMP approach to sequenced copolymers, which offers unique advantages over step-growth methods, should prove applicable to other sequences of α-hydroxy acids and to monomers beyond those described in this paper. It should be possible to execute ED-ROMP on any sequence that can be incorporated into an olefin-bearing macrocycle, a process greatly facilitated by the known propensity of RCM to generate large rings.[171] Although monomer production is somewhat limited by the need for high dilution, the production of gram-scale quantities sufficient for laboratory studies is not challenging. The tolerance of RCM for functional groups and the generality of the reaction should also make it possible to design the

olefin-containing linker unit of the resulting copolymers to be compatible with the targeted properties and applications. Future studies will explore further the generality of this approach.

4.4 EXPERIMENTAL

4.4.1 General information

All experiments were carried out in oven-dried glassware under an atmosphere of N_2 using standard Schlenk line techniques. N,N'-dicyclohexylcarbodiimide (DCC) was purchased from Oakwood Chemical and used without further purification. 10% Pd/C was purchased from Alfa Aesar. Palladium, 10 wt% (dry basis) on activated carbon, wet, Degussa type E101 NE/W was purchased from Sigma Aldrich. Ethylene glycol (Eg) was purchased from Mallinckrodt and used without further purification. Methylene chloride (CH_2Cl_2, Fisher) and ethyl acetate (EtOAc, Sigma Aldrich) were purified by a Solvent Dispensing System by J. C. Meyer. Both were passed over two columns of neutral alumina. Anhydrous, inhibitor-free tetrahydrofuran (THF, $\geq$99.9%) and Grubb's 2nd generation catalyst were purchased from Sigma Aldrich. Column chromatography was performed using Sorbent Technologies 60 Å, 40-63 μm standard grade silica. **C-SiR$_3$**,[17,60] 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS),[82] **Bn-G**, **Bn-L**, **L-SiR$_3$**, and **Bn-GL-SiR$_3$** were prepared according previously-published protocols.[15,59] Ring-closing metathesis reactions were performed according to a modified preparation from Matsuya et al.[173] All other chemicals were used without further purification.

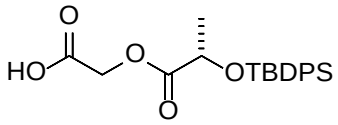
4.4.2 Compound characterization

^{1}H (300, 400, 600, and 700 MHz) and ^{13}C (75, 100, 150, and 175 MHz) spectra were obtained using Bruker spectrometers and are reported as δ values in ppm relative to the reported solvent ($CDCl_3$ referenced to 7.24). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and combinations thereof.

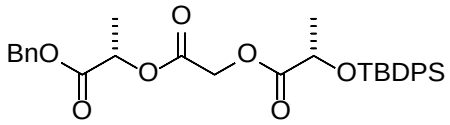
HRMS data were obtained on a LC/Q-TOF instrument. Molecular weights and dispersities were obtained on a Waters GPC (THF) with Jordi 500, 1000, and 10000 Å divinyl benzene columns, and refractive index detector (Waters) was calibrated to polystyrene standards. Absolute molecular weight and dispersity data was obtained using a Viscotek multi-detector system (THF) consisting of a GPCmax VE2001 autosampler, VE 3580 RI detector, and 270 dual detector equipped with a right angle light scattering detector and viscometer. The column series consisted of Waters Styragel HR1, HR3, and HR4E styrene-divinylbenzene columns packed with 5 μm particles. Column and multi-detector calibration was completed using a narrow polystyrene standard and verified with a broad polystyrene standard. The sample injection volume of 100 μL was run through the system at a rate of 0.50 mL/min.

Differential scanning calorimetry was performed with a TA Instruments Q200 on polymers containing **L** and **G** monomers. Samples were prepared by first dissolving in CH_2Cl_2, dropcast into aluminum pans, and put under vacuum overnight. The samples were then annealed at 85 ^{o}C for 3 h. Each run had a heating and cooling rate of 10 ^{o}C/min. Differential scanning calorimetry of copolymers containing **L** and **C** were performed on a Perkin Elmer DSC 6000 equipped with a Perkin Elmer Intracooler. T_gs were collected in the in the first heating cycle.

4.4.3 Synthesis of cyclic macromonomers and copolymers

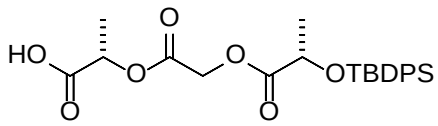


GL-SiR$_3$. To a stirring solution of Bn-GL-SiR$_3$ (34.05 g, 71.44 mmol) in EtOAc (700 mL) under N_2 was added 10% Pd/C (3.41 g, 10% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5-25% EtOAc in hexanes) to provide the product as a colorless liquid (27.61 g, 87.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1H), 7.66-7.65 (m, 4H), 7.44-7.32 (m, 6H), 4.58 (d, J = 16.4 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H), 4.38 (q, J = 6.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.03, 172.79, 135.89, 135.73, 133.39, 132.89, 129.84, 127.67, 127.61, 68.60, 59.98, 26.77, 21.23, 19.21; HRMS (M-H$^+$) calc mass 385.14713, found 385.14768.

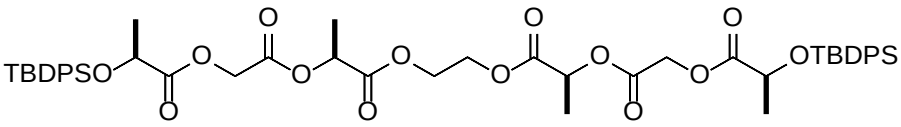


Bn-LGL-SiR$_3$. To a stirring solution of Bn-L (11.57 g, 64.21 mmol, 1.1 equiv.) and GL-SiR$_3$ (22.56 g, 58.37 mmol, 1 equiv.), in CH_2Cl_2 (290 mL) was added DPTS (13.25 g, 64.21 mmol, 0.2 equiv.). Once the mixture became homogeneous, DCC (13.25 g, 64.21 mmol, 1.1 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5-25% EtOAc in hexanes) to provide the product as a colorless liquid (32.03 g, 92.9%). ^{1}H NMR

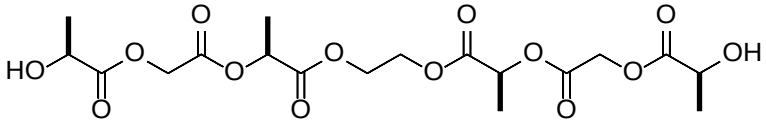
(400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.44-7.30 (m, 11H), 5.18 (q, J = 7.2 Hz, 1H), 5.17 (d, J = 14.0 Hz, 1H), 5.14 (d, J = 14.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.37 (d, J = 6.8 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.99, 169.90, 166.86, 135.90, 135.73, 135.14, 133.41, 132.96, 129.81, 128.61, 128.45, 128.14, 127.66, 127.60, 69.28, 68.80, 67.16, 60.29, 26.78, 21.27, 19.21, 16.80; HRMS ($M+NH_4^+$) calc mass 566.2574, found 566.2578.



LGL-SiR$_3$. To a stirring solution of Bn-LGL-SiR_3 (13.86 g, 25.3 mmol) in EtOAc (250 mL) under N_2 was added 10% Pd/C (5% w/w, 1.41 g). The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm H_2. The vessel was placed under N_2, filtered over celite, and concentrated *in vacuo*. The product was a colorless liquid (11.58 g, quantitative). ^1H NMR (400 MHz, $CDCl_3$) δ 11.13 (br s, 1H), 7.66-7.64 (m, 4H), 7.43-7.32 (m, 6H), 5.16 (q, J = 7.2 Hz, 1H), 4.65 (d, J = 16 Hz, 1H), 4.42 (d, J = 16 Hz, 1H), 4.36 (q, J = 6.8 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.96, 173.08, 166.82, 135.89, 135.72, 133.38, 132.93, 129.82, 127.65, 127.60, 68.70, 68.59, 60.23, 26.77, 21.26, 19.20, 16.67; HRMS ($M+H^+$) calc mass 457.16771, found 457.16838.

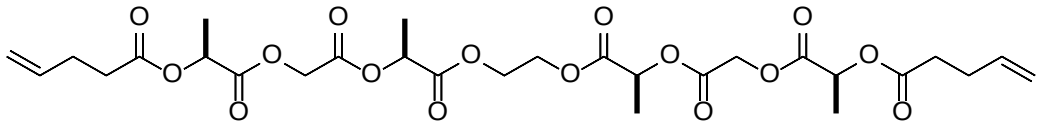


Eg-(LGL-SiR$_3$)$_2$. To a stirring solution of ethylene glycol (0.76 g, 12.2 mmol, 1 equiv.) and LGL-SiR$_3$ (11.66 g, 25.4 mmol, 2.1 equiv.) in CH_2Cl_2 (120 mL) was added DPTS (1.43 g, 4.85 mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (5.45 g, 26.4 mmol, 2.2 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 7.5-20% EtOAc in hexanes) to provide the product as a colorless liquid (11.27 g, 98.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 8H), 7.44-7.31 (m, 12H), 5.12 (q, J = 7.1 Hz, 2H), 4.64 (d, J = 16.0 Hz, 2H), 4.42 (d, J = 16.0 Hz, 2H), 4.36 (q, J = 6.8 Hz, 2H), 4.37-4.27 (m, 4H), 1.45 (d, J = 7.2 Hz, 6H), 1.40 (d, J = 6.8 Hz, 6H), 1.07 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.98, 169.75, 166.82, 135.88, 135.71, 133.38, 132.95, 129.81, 127.65, 127.59, 69.09, 68.58, 62.69, 60.24, 26.77, 21.26, 19.20, 16.70; HRMS ($M+NH_4^+$) calc mass 960.4022, found 960.4017.



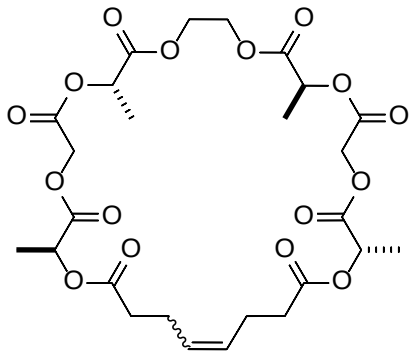
Eg-(LGL)$_2$. To a stirring solution of Eg-(LGL-SiR$_3$)$_2$ (3.16 g, 3.33 mmol, 1 equiv.) in THF (83 mL) at 0 ^{o}C under N_2 was slowly added acetic acid (3.0 mL, 53 mmol, 16 equiv.) and then tetrabutylammonium fluoride (1.0 M in THF, 10.0 mL, 9.98 mmol). The reaction was stirred at 0 ^{o}C overnight, then the ice bath was removed and stirring continued at RT for an additional day. After cooling the reaction mixture to 0 ^{o}C, brine (150 mL) was added. The resulting aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL), the combined organic layers were washed with

aqueous saturated sodium bicarbonate solution (150 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 25-75% EtOAc in hexanes as the eluent to provide the product as a white solid (1.55 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (q, J = 7.1 Hz, 2H), 4.80 (d, J = 16.0 Hz, 2H), 4.72 (d, J = 16.0 Hz, 2H), 4.41-4.31 (m, 6H), 2.89 (br s, 2H), 1.50 (d, J = 6.8 Hz, 6H), 1.46 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.82, 169.71, 166.73, 69.39, 66.72, 62.78, 60.83, 20.22, 16.69; HRMS ($M+NH_4^+$) calc mass 484.1666, found 484.1627.

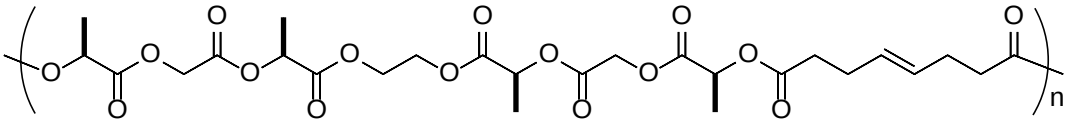


Eg-(LGL-P)$_2$. To a stirring solution of Eg-$(LGL)_2$ (2.74 g, 5.88 mmol, 1 equiv.) and 4-pentenoic acid (1.32 mL, 12.9 mmol, 2.2 equiv.) in CH_2Cl_2 (60 mL) was added DPTS (0.70 g, 2.37 mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (5.45 g, 26.4 mmol, 2.2 equiv.) was added and the reaction was allowed to stir overnight. The reaction was filtered to remove the urea byproduct, the filtrate was diluted with CH_2Cl_2 (140 mL), washed with 1 M HCl (100 mL), and washed with sat. $NaHCO_3$ (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 80 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless solid (3.10 g, 83.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.9, 10.5, 6.4 Hz, 2H), 5.15 (q, J = 7.1 Hz, 2H), 5.15 (q, J = 7.1 Hz, 2H), 5.04 (ddt, J = 17.1, 1.6, 1.6 Hz, 2H), 4.98 (ddt, J = 10.2, 1.4, 1.3 Hz, 2H), 4.84 (d, J = 16.0 Hz, 2H), 4.61 (d, J = 16.0 Hz, 2H), 4.38-4.30 (m, 4H), 2.54-2.45 (m, 4H), 2.43-2.34 (m, 4H), 1.53 (d, J = 6.8 Hz, 6H), 1.49 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31, 170.20, 169.69, 169.59, 136.40,

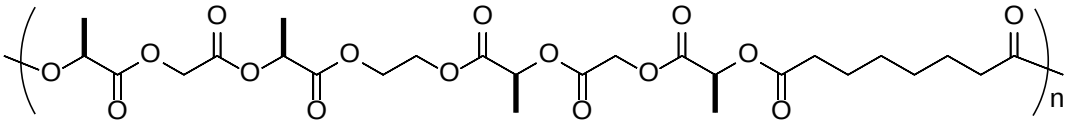
115.60, 69.24, 68.16, 62.74, 60.67, 33.09, 28.62, 16.84, 16.70; HRMS ($M+H^+$) calc mass 631.22326, found 631.22530.



***cyclic*-Eg-(LGL-P)$_2$**. A solution of Grubbs' 2nd generation catalyst (3.9 mg, 0.0046 mmol) in CH_2Cl_2 (1 mL) was added to a stirring solution of Eg-(LGL-P)$_2$ (28.0 mg, 0.044 mmol) in CH_2Cl_2 (42 mL). An additional 1 mL of CH_2Cl_2 was used to rinse the vial that had contained the catalyst solution, and the reaction was allowed to stir at RT overnight. The reaction was quenched by adding 1 mL ethyl vinyl ether, and then concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 20-30% EtOAc in hexanes) to provide the product as a colorless liquid with an *E/Z* ratio of 5.1/1 (24.1 mg, 89.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44-5.23 (*trans*) and 5.39-5.38 (*cis*) (m, 2H), 4.79 (*trans*) and 4.77 (*cis*) (d, J = 16 Hz, 2H), 4.675 (*trans*) and 4.67 (*cis*) (d, J = 16.0 Hz, 2H), 4.38-4.31 (m, 4H), 2.44-2.41 (m, 4H), 2.39-2.26 (m, 4H), 1.52 (d, J = 7.2 Hz, 6H), 1.50 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.27 (*cis)*, 172.22 (*trans*), 170.19 (*trans*), 170.15 (*cis*), 169.76, 166.61, 129.32 (*trans*), 128.97 (*cis*), 69.35, 68.19 (*cis*), 68.10 (*trans*), 62.71 (*trans*), 62.63 (*cis*), 60.86 (*cis*), 60.77 (*trans*), 33.80 (*cis*), 33.62 (*trans*), 27.56, 27.34, 22.75, 16.85 (*trans*), 16.78 (*cis*), 16.69 (*trans*), 16.65 (*cis*); HRMS ($M+H^+$) calc mass 603.19251, found 603.19028.

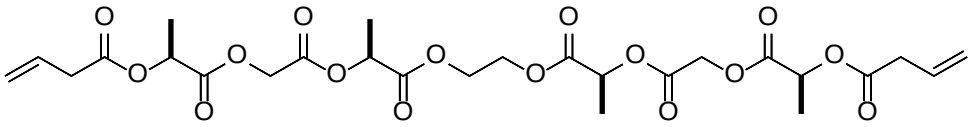


Poly (LGL-Eg-LGL-Oed). Grubbs' 2nd generation catalyst (10.5 mg, 0.012 mmol) was dissolved in CH_2Cl_2 (0.3 mL) and added via syringe to a stirring solution of ***cyclic*-Eg-(LGL-P)$_2$** (0.57 g, 0.94 mmol) in CH_2Cl_2 (1.0 mL). The reaction was allowed to stir at RT for 4 h before being quenched through the addition of ethyl vinyl ether (0.2 mL). The reaction mixture was dissolved in a minimal amount of CH_2Cl_2 and precipitated into 250 mL stirring MeOH. The solid was isolated, dissolved in a minimal amount of CH_2Cl_2, precipitated in 175 mL of stirring MeOH, and dried under vacuum overnight to yield an off-white solid with an *E/Z* ratio of 5.4/1 (0.42 g, 74.8%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.50-5.41 (*trans*), 5.39-5.36 (*cis*) (m, 2H), 5.15 (q, J = 7 Hz, 2H), 5.13 (q, J = 7 Hz, 2H), 4.84 (d, J = 16.1 Hz, 2H), 4.60 (d, J = 16,1 Hz, 2H), 4.38-4.29 (m, 4H), 2.46-2.36 (m, 4H), 2.38-2.29 (m, 4H), 1.53 (d, J = 7.0 Hz, 6H), 1.49 (d, J = 7.0 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.32 (*trans*), 172.21 (*cis*), 170.21, 169.75 (*cis*), 169.69 (*trans*), 166.60, 69.34 (*cis*), 69.22 (*trans*), 62.74 (*trans*), 62.71 (*cis*), 60.76 (*cis*), 60.64 (*trans*), 33.64 (*trans*), 33.61 (*cis*), 27.53 (*trans*), 22.47 (*cis*), 16.83 (*trans*), 16.79 (*cis*), 16.69 (*trans*), 16.64 (*cis*); DSC: T_g = 18 ^{o}C; SEC (THF): M_n = 33.3 kDa, M_w = 44.5 kDa, Đ = 1.3.



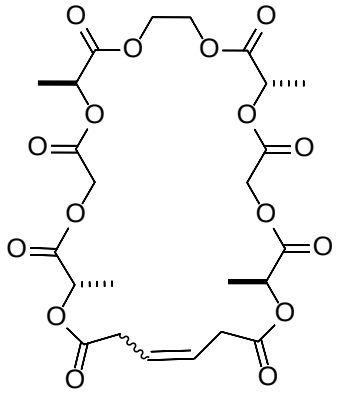
Poly (LGL-Eg-LGL-Od). A dried three-neck round bottom flask with two gas adapters was charged with THF (29.7 mL) and Poly (LGL-Eg-LGL-Oed) (0.124 g, 0.21 mmol with respect to the repeat unit). Once the polymer had dissolved, Degussa's catalyst (0.25 g) was added and the reaction vessel was purged two times with H_2. Stirring continued overnight under 1 atm H_2. The

flask was then filled with N_2 and the mixture was filtered over a layered, thick pad of celite and activated carbon. The filtrate was filtered over a short plug of celite and concentrated *in vacuo* to yield a colorless solid (0.123 g, 98.8%, 98.6% conversion). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.54-5.52 (m, 0.02), 5.14 (q, J = 7.1 Hz, 2H), 5.12 (q, J = 7.1 Hz, 2H), 4.85 (d, J = 16.0 Hz, 2H), 4.60 (d, J = 16.4 Hz, 2H), 4.38-4.30 (m, 4H), 2.38 (dt, J = 15.6, 7.5 Hz, 2H), 2.33 (dt, J = 16.0, 7.5 Hz, 2H), 1.70-1.58 (m, 4H), 1.53 (d, J = 7.2 Hz, 6H), 1.49 (d, J = 7.2 Hz, 6H), 1.36-1.29 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.97, 170.30, 169.71, 166.62, 69.20, 68.03, 62.73, 60.61, 33.69, 28.56, 28.31, 24.47, 16.82, 16.69; DSC: T_g = 13 ^{o}C; SEC (THF): M_n = 27.9 kDa, M_w = 41.4 kDa, Đ = 1.5.

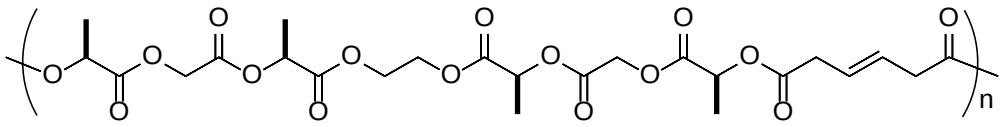


Eg-(LGL-B)$_2$. To a stirring solution of Eg-$(LGL)_2$ (0.113 g, 0.243 mmol, 1 equiv.), 3-butenoic acid (0.05 mL, 0.588 mmol, 2.4 equiv.) in CH_2Cl_2 (2.4 mL) was added DPTS (0.029 g, mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (0.112 g, 0.542 mmol, 2.2 equiv.) was added and the reaction was allowed to stir overnight. The reaction was filtered to and the filtrate was diluted with CH_2Cl_2 (50 mL), washed with 1 M HCl (50 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 25 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 17.5-20% EtOAc in hexanes) to provide the product as a colorless liquid (0.116 g, 79.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, J = 17.0, 10.4, 6.8 Hz, 2H), 5.20-5.12 (m, 8H), 4.84 (d, J = 16.0 Hz, 2H), 4.61 (d, J = 16.0 Hz, 2H), 4.38-4.30 (m, 4H), 3.21-3.10 (m, 4H), 1.54 (d, J = 6.8 Hz, 6H), 1.49 (d, J = 6.8 Hz, 6H); ^{13}C NMR

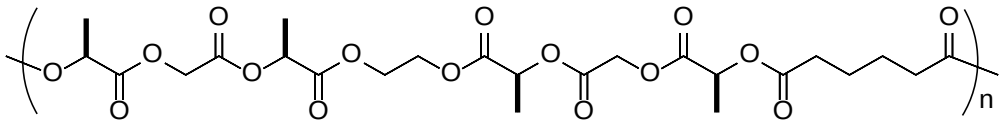
(100 MHz, $CDCl_3$) δ 170.82, 170.08, 169.69, 166.57, 129.59, 118.94, 69.24, 68.38, 62.73, 60.69, 38.55, 16.78, 16.69; HRMS ($M+H^+$) calc mass 603.19251, found 603.19073.



***cyclic*-Eg-(LGL-B)$_2$**. A solution of Grubbs' 2nd generation catalyst (52.7 mg, 0.062 mmol) in CH_2Cl_2 (1 mL) was added to a stirring solution of Eg-(LGL-B)$_2$ (0.37 g, 0.62 mmol) in CH_2Cl_2 (620 mL). An additional 1 mL of CH_2Cl_2 was used to rinse the vial that had contained the catalyst solution, and the reaction was allowed to stir at RT overnight. The reaction was quenched by adding 1 mL ethyl vinyl ether, and then concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 25-30% EtOAc in hexanes) to provide the product as a colorless liquid with an *E/Z* ratio of 3.9/1 (0.29 g, 81.4%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.79-5.78 (*cis*) and 5.75-5.72 (*trans*) (m, 2H), 5.20 (*cis*) and 5.20 (*trans*) (q, J = 7.2 Hz, 2H), 5.15 (q, J = 7.2 Hz, 2H), 4.76 (*cis*) and 4.75 (*trans*) (d, J = 16.0 Hz, 2H), 4.66 (d, J = 16.0 Hz, 2H), 4.41-4.32 (m, 4H), 3.29-3.05 (m, 4H), 1.51 (d, J = 7.2 Hz, 6H), 1.49 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.52 (*trans*), 170.33 (*cis*), 169.85 (*trans*), 169.81 (*cis*), 169.71 (*trans*), 166.49, 125.67 (*trans*), 124.66 (*cis*), 69.42, 68.49 (*cis*), 68.38 (*trans*), 62.59 (*cis*), 62.52 (*trans*), 60.88, 37.38 (*trans*), 32.66 (*cis*), 21.01, 16.74 (*trans*), 16.68 (*cis*), 16.62 (*trans*); HRMS ($M+H^+$) calc mass 575.16066, found 575.15986.



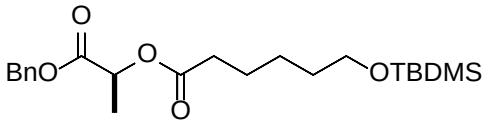
Poly (LGL-Eg-LGL-Hed). Grubbs' 2nd generation catalyst (5.8 mg, 0.0069 mmol) was dissolved in 0.28 mL CH_2Cl_2, added via syringe to a stirring solution of *cyclic*-Eg-(LGL-B)$_2$ (0.31 g, 0.55 mmol) was dissolved in CH_2Cl_2 (0.5 mL). The reaction was allowed to stir at RT for 4 h before being quenched through the addition of ethyl vinyl ether (0.2 mL). The reaction mixture was dissolved in a minimal amount of CH_2Cl_2 and precipitated into 125 mL stirring MeOH. The solid was isolated, redissolved in minimal CH_2Cl_2 and reprecipitated in 100 mL of stirring MeOH. The solid was dried under vacuum overnight to yield an off-white solid with an *E/Z* ratio of 4.7/1 (0.26 g, 81.8%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.82-5.76 (*cis*) and 5.72-5.67 (*trans*) (m, 2H), 5.15 (q, J = 7.0 Hz, 2H), 5.13 (q, J = 7.0 Hz, 2H), 4.84 (d, J = 16.1 Hz, 2H), 4.61 (d, J = 16.1 Hz, 2H), 4.38-4.31 (m, 4H), 3.19-3.13 (m, 4H), 1.54 (d, J = 7 Hz, 6H), 1.49 (d, J = 7 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.80, 170.48 (*cis*), 170.07, 170.04 (*cis*), 169.70, 166.58, 125.68 (*trans*), 124.24 (*cis*), 69.22, 68.51 (*cis*), 68.43 (*trans*), 62.74, 60.67, 37.24, 32.60 (*cis*), 16.78, 16.70; DSC: T_g = 32 ^{o}C; SEC (THF): M_n = 33.4 kDa, M_w = 46.0 kDa, Đ = 1.4.



Poly (LGL-Eg-LGL-Hd). A dried three-neck round bottom flask with two gas adapters was charged with THF (30.2 mL) and Poly (LGL-Eg-LGL-Hed) (0.121 g, 0.21 mmol with respect to the repeat unit). Once the polymer had dissolved, Degussa's catalyst (0.25 g) was added and the reaction vessel was purged two times with H_2. Stirring continued overnight under 1 atm H_2. The flask was then filled with N_2 and the mixture was filtered over a layered, thick pad of celite and

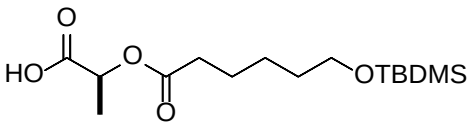
activated carbon. The filtrate was then filtered over a short plug of celite and concentrated *in vacuo* to yield a colorless solid (0.112 g, 92.4%, 96.6% conversion). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.81-5.76 (*cis*) and 5.72-5.67 (*trans*) (m, 0.06H), 5.14 (q, J = 7.0 Hz, 2H), 5.12 (q, J = 7.0 Hz, 2H), 4.85 (d, J = 16.1 Hz, 2H), 4.61 (d, J = 16.1 Hz, 2H), 4.7-4.31 (m, 4H), 2.43-2.35 (m, 4H), 1.71-1.65 (m, 4H), 1.53 (d, J = 7.0 Hz, 6H), 1.49 (d, J = 7.0 Hz, 6H); DSC: T_g = 23 ^{o}C; SEC (THF): M_n = 27.1 kDa, M_w = 41.7 kDa, Đ = 1.5.

Poly (LGL-Eg-LGL-Oed) polymerization kinetics study. The LGL-macromonomer was added to a vial and charged with a stir bar and appropriate amount of CH_2Cl_2 under N_2. Once dissolved, a solution of Grubbs' 2nd generation catalyst (1.25 mol%) in CH_2Cl_2 (0.7 M with respect to monomer, final concentration) was added and the reaction mixture was allowed to stir for given time. The reaction was then quenched with ethyl vinyl ether (0.1 mL). For two of the polymerizations (6 and 7), aliquots were removed at different time points. For reaction 6, aliquots was removed at 60 min (6) and 120 min (8) and quenched and then the rest of the reaction mixture was quenched at time 240 min (10). For reaction 7, an aliquot was removed at 90 min (7) and quenched and then the rest of the reaction mixture was quenched at time 180 min (9).

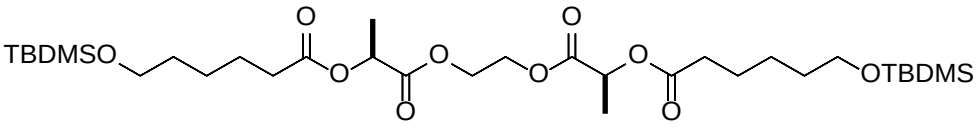


Bn-LC-SiR$_3$. To a stirring solution of Bn-L (6.46 g, 35.8 mmol, 1.1 equiv.) and C-SiR_3 (7.72 g, 31.3 mmol, 1 equiv.) in CH_2Cl_2 (325 mL) was added DPTS (1.86 g, 6.32 mmol, 0.2 equiv.). Once the mixture became homogeneous, DCC (7.13 g, 34.5 mmol, 1.1 equiv.) was added and the

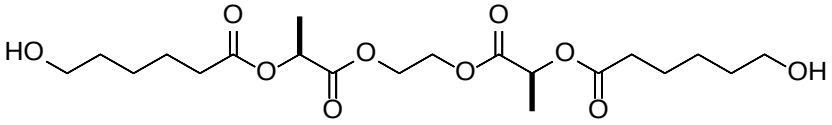
reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (12.80 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.18 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.12 (q, J = 7.0 Hz, 1H), 3.57 (t, J = 6.3 Hz, 2H), 2.36 (dt, J_1 = 15.6 Hz, J_2 = 7.8 Hz, 1H), 2.35 (dt, J_1 = 15.6 Hz, J_2 = 7.4 Hz, 1H), 1.68-1.58 (m, 2H), 1.53-1.46 (m, 2H), 1.47 (d, J = 7.0 Hz, 3H), 1.39-1.29 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.04, 170.72, 135.35, 128.56, 128.35, 128.10, 68.38, 66.91, 62.92, 33.94, 32.42, 25.94, 25.33, 24.61, 18.32, 16.89, -5.31; HRMS (M+Na) calc mass 431.2230, found 431.2240.



LC-SiR$_3$. Bn-LC-SiR_3 (8.74 g, 21.4 mmol) and 10% Pd/C (0.44 g, 5% w/w) were added to a stirring solution of EtOAc (215 mL, 0.1 M in substrate) under N_2. The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (6.20 g, 91.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 5.08 (q, J = 7.1 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 2.37 (dt, J_1 = 15.6 Hz, J_2 = 7.7 Hz, 1H), 2.36 (dt, J_1 = 15.9 Hz, J_2 = 7.5 Hz, 1H), 1.70-1.60 (m, 2H), 1.56-1.47 (m, 2H), 1.50 (d, J = 7.1 Hz, 3H), 1.40-1.33 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.30, 173.09, 67.90, 63.00, 33.86, 32.40, 25.94, 25.31, 24.56, 18.34, 16.80, -5.30; HRMS (M+Na) calc mass 341.1760, found 341.1745.

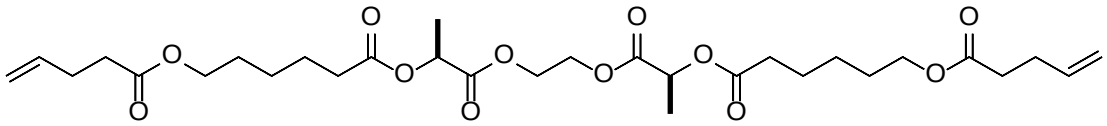


Eg-(LC-SiR$_3$)$_2$. To a stirring solution of ethylene glycol (0.60 g, 9.73 mmol, 1 equiv.) and LC-SiR$_3$ (6.50 g, 20.4 mmol, 2.1 equiv.) in CH_2Cl_2 (100 mL) was added DPTS (1.14 g, 3.88 mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (4.21 g, 20.4 mmol, 2.1 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5-7.5% EtOAc in hexanes) to provide the product as a colorless liquid (6.38 g, 99.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (q, J = 7.1 Hz, 2H), 4.38-4.25 (m, 4H), 3.58 (t, J = 6.4 Hz, 4H), 2.37 (dt, J_1 = 15.6 Hz, J_2 = 7.6 Hz, 2H), 2.36 (dt, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 2H), 1.69-1.61 (m, 4H), 1.55-1.47 (m, 4H), 1.46 (d, J = 7.2 Hz, 6H), 1.40-1.33 (m 4H), 0.87 (s, 18H), 0.02 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.97, 170.67, 68.21, 62.94, 62.57, 33.91, 32.45, 25.96, 25.38, 24.62, 18.33, 16.85, -5.30; HRMS ($M+H^+$) calc mass 663.39543, found 663.39517.

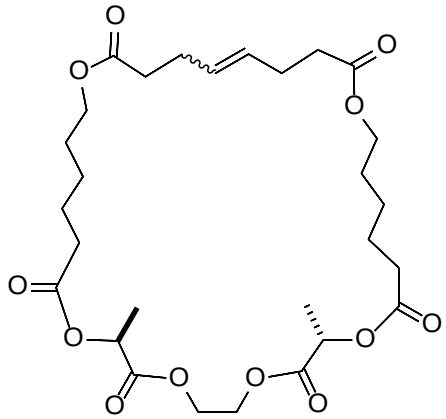


Eg-(LC)$_2$. Eg-(LC-SiR$_3$)$_2$ (2.04 g, 3.08 mmol), acetic acid (2.8 mL, 49.2 mmol, 16 equiv.), and tetrabutylammonium fluoride (1 M in THF, 9.2 mL, 3 equiv.) were combined in THF (30 mL) and stirred overnight. The reaction mixture was then partitioned between 50 mL brine and 25 mL of diethyl ether and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 25 mL) and the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (50 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The crude

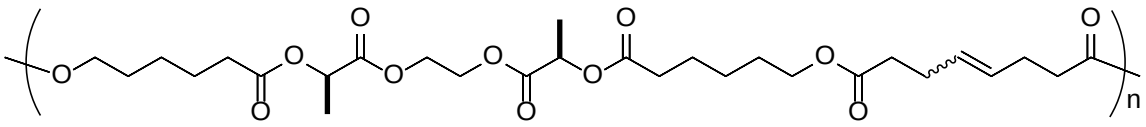
material was purified by flash chromatography (SiO_2, 50% EtOAc in hexanes) to provide the product as a colorless solid (1.16 g, 86.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (q, J = 7.1 Hz, 2H), 4.38-4.25 (m, 4H), 3.63-3.60 (m, 4H), 2.39 (dt, J_1 = 15.6 Hz, J_2 = 7.6 Hz, 2H), 2.38 (dt, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 2H), 1.70-1.62 (m, 6H), 1.60-1.53 (m, 4H), 1.47 (d, J = 7.2 Hz, 6H), 1.44-1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.99, 170.67, 68.25, 62.58, 62.46, 33.76, 32.19, 25.05, 24.42, 16.82; HRMS (M+Na) calc mass 457.2050, found 457.2053.



Eg-(LC-P)$_2$. To a stirring solution of Eg-$(LC)_2$ (0.57 g, 1.3 mmol, 1 equiv.) and 4-pentenoic acid (0.3 mL, 3 mmol, 2.3 equiv.) in CH_2Cl_2 (15 mL) was added DPTS (0.16 g, 0.54 mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (0.60 g, 2.9 mmol, 2.2 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 10-15% EtOAc in hexanes) to provide the product as a colorless solid (0.79 g, 99.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.8, 10.4, 6.4 Hz, 2H), 5.06 (q, J = 7.2 Hz, 2H), 5.03 (m, 2H), 4.97 (m, 2H), 4.37-4.28 (m, 4H), 4.05 (t, J = 6.6 Hz, 4H), 2.43-2.29 (m, 12H), 1.69-1.59 (m, 8H), 1.46 (d, J = 7.2 Hz, 6H), 1.42-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.06, 172.76, 170.54, 136.68, 115.43, 68.23, 64.12, 62.56, 33.68, 33.51, 28.85, 28.27, 25.39, 24.36, 16.82; HRMS ($M+H^+$) calc mass 599.3068, found 599.3061.



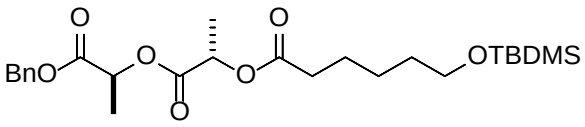
***cyclic*-Eg-(LC-P)$_2$**. A solution of Grubbs' 2nd generation catalyst (2.9 mg, 0.0034 mmol) in CH_2Cl_2 (1 mL) was added to a stirring solution of Eg-(LC-P)$_2$ (19 mg, 0.032 mmol) in CH_2Cl_2 (324 mL). An additional 1 mL of CH_2Cl_2 was used to rinse the vial that had contained the catalyst solution, and the reaction was allowed to stir at RT overnight. The reaction was quenched by adding 1 mL ethyl vinyl ether, and then concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 20-30% EtOAc in hexanes) to provide the product as a colorless liquid with an *E/Z* ratio of 2.8/1 (16.8 mg, 91.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.43 (*trans*) and 5.41-5.34 (*cis*) (m, 2H), 5.07 (q, J = 7.1 Hz, 2H), 4.37-4.29 (m, 4H), 4.06 (*cis*) and 4.05 (*trans*) (t, J = 6.4 Hz, 4H), 2.38 (dt, J_1 = 15.6 Hz, J_2 = 7.2 Hz, 2H), 2.37-2.28 (m, 10H), 1.70-1.58 (m, 8H), 1.47 (d, J = 7.2 Hz, 6H), 1.45-1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.06, 172.73, 170.54, 129.41 (*trans*), 129.04 (*cis*), 68.32, 64.13, 64.07, 62.55, 34.38, 34.17, 33.67, 29.68, 28.30, 28.27, 27.79, 25.45, 25.40, 24.41, 24.37, 22.90, 16.82; HRMS (M+Na) calc mass 593.2574, found 593.2565.



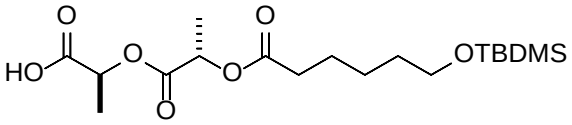
Poly (CL-Eg-LC-Oed) varying catalyst amount study:

Poly (CL-Eg-LC-Oed)-1. Grubbs' 2nd generation catalyst (2.3 mg, 0.0027 mmol, 1.29 mol%) was dissolved in CH_2Cl_2 (0.1 mL), and to a stirring solution of *cyclic*-Eg-(LC-P)$_2$ (0.12 g, 0.21 mmol) in CH_2Cl_2 (0.21 mL). The reaction was allowed to stir at RT for 3 h before being quenched through the addition of ethyl vinyl ether (0.2 mL). An aliquot was removed from the polymerization and dried under vacuum overnight to yield an off-white solid (6.0 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.47-5.40 (*trans*) and 5.36-5.35 (*cis*) (m, 2H), 5.06 (q, J = 7.0 Hz, 2H), 4.37-4.29 (m, 4H), 4.05-4.02 (m, 4H), 2.42-2.25 (m, 12H), 1.68-1.59 (m, 8H), 1.46 (d, J = 6.6 Hz, 6H), 1.41-1.36 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.10, 172.78, 170.56, 129.38 (*trans*), 128.97 (*cis*), 68.31 (*cis*), 68.22 (*trans*), 64.16 (*cis*), 64.10 (*trans*), 62.57, 34.15 (*cis*), 34.10 (*trans*), 33.67, 28.28, 27.77, 25.44 (*cis*), 25.38 (*trans*), 24.36, 22.68, 16.83; DSC: T_g = -27.3 ^{o}C; SEC (THF): M_n = 25.9 kDa, M_w = 32.4 kDa, Đ = 1.25.

Poly (CL-Eg-LC-Oed)-2. Grubbs' 2nd generation catalyst (1.2 mg, 0.0014 mmol, 0.61 mol%) was dissolved in CH_2Cl_2 (0.1 mL) added via syringe to a stirring solution of *cyclic*-Eg-(LC-P)$_2$ (0.13 g, 0.23 mmol) in CH_2Cl_2 (0.22 mL). The reaction was allowed to stir at RT for 3 h before being quenched through the addition of ethyl vinyl ether (0.2 mL). An aliquot was removed from the polymerization and dried under vacuum overnight to yield an off-white solid (7.6 mg). DSC: T_g = -27.2 ^{o}C; SEC (THF): M_n = 38.8 kDa, M_w = 48.1 kDa, Đ = 1.25.

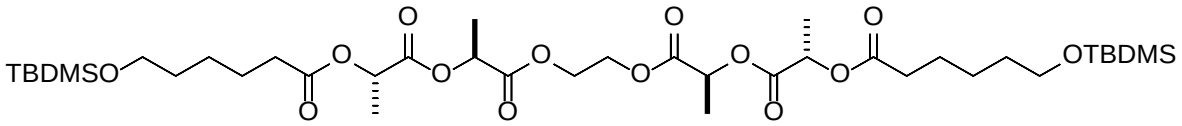


Bn-LLC-SiR$_3$. To a stirring solution of Bn-L (2.92 g, 16.2 mmol, 1.1 equiv.) and LC-SiR$_3$ (4.66 g, 14.6 mmol, equiv.) in CH_2Cl_2 (150 mL) was added DPTS (0.87 g, 2.94 mmol, 0.2 equiv.). Once the mixture became homogeneous, DCC (3.18 g, 15.4 mmol, 1.1 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to provide the product as a colorless liquid (6.54 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.18 (q, J = 7.1 Hz, 1H), 5.17 (d, J = 12.3 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.07 (q, J = 7 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 2.37 (dt, J_1 = 15.6 Hz, J_2 = 7.7 Hz, 1H), 2.36 (dt, J_1 = 15.9 Hz, J_2 = 7.5 Hz, 1H), 1.69-1.59 (m, 2H), 1.55-1.46 (m, 2H), 1.51 (d, J = 7.2 Hz, 3H), 1.47 (d, J = 7.2 Hz, 3H), 1.40-1.30 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.12, 170.33, 170.09, 135.10, 128.59, 128.46, 128.22, 69.03, 68.12, 67.13, 62.93, 33.85, 32.42, 25.94, 25.31, 24.57, 18.32, 16.78, 16.69, -5.31; HRMS (M+Na) calc mass 503.2441, found 503.2395.

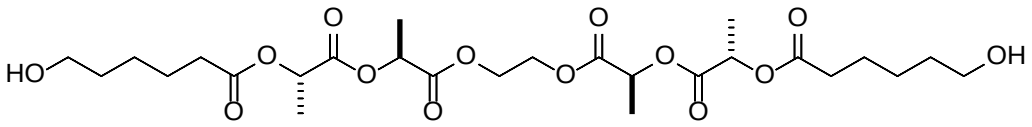


LLC-SiR$_3$. Bn-LLC-SiR$_3$ (6.35 g, 13.2 mmol) was combined with 10% Pd/C (0.31 g, 5 % w/w) in EtOAc (135 mL, 0.1 M in substrate) and stirred under N_2. The reaction vessel was evacuated and purged twice with a 1 atm H_2 balloon. The reaction was allowed to stir overnight under 1 atm H_2. The vessel was placed under N_2, filtered over celite, and concentrated *in vacuo*. The concentrate was chromatographed over silica using 10% EtOAc in hexanes as the eluent. The

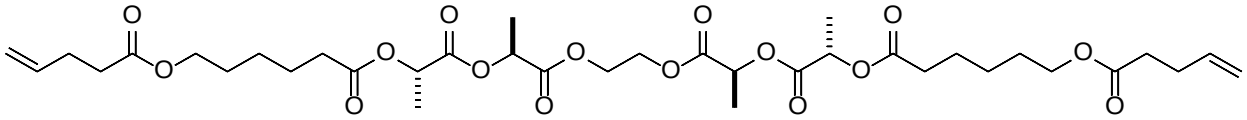
product was a colorless liquid (4.22 g, 81.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (br s, 1H), 5.17 (q, J = 7.1 Hz, 1H), 5.09 (q, J = 7.2 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 2.38 (dt, J_1 = 15.6 Hz, J_2 = 7.6 Hz, 1H), 2.37 (dt, J_1 = 15.6 Hz, J_2 = 7.4 Hz, 1H), 1.68-1.61 (m, 2H), 1.55-1.47 (m, 2H), 1.54 (d, J = 7.2 Hz, 3H), 1.52 (d, J = 7.2 Hz, 3H), 1.40 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.27, 173.21, 170.26, 68.57, 68.15, 63.03, 33.85, 32.36, 25.95, 25.31, 24.58, 18.34, 16.70, 16.68, -.531; HRMS ($M-H^+$) calc mass 389.1996, found 389.2010.



Eg-(LLC-SiR$_3$)$_2$. To a stirring solution of ethylene glycol (0.26 g, 4.15 mmol, 1 equiv.) and LLC-SiR_3 (3.96 g, 10.2 mmol, 2.1 equiv.) in CH_2Cl_2 (42 mL) was added DPTS (0.24 g, 0.82 mmol, 0.2 equiv.). Once the mixture became homogeneous, DCC (1.77 g, 8.57 mmol, 2.1 equiv.) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 10% EtOAc in hexanes) to provide the product as a colorless liquid (2.74 g, 81.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (q, J = 7.2 Hz, 2H), 5.08 (q, J = 7.2 Hz, 2H), 4.38-4.27 (m, 4H), 3.58 (t, J = 6.5 Hz, 4H), 2.37 (dt, J_1 = 15.9 Hz, J_2 = 7.8 Hz, 2H), 2.36 (dt, J_1 = 15.6 Hz, J_2 = 7.5 Hz, 2H), 1.69-1.59 (m, 4H), 1.56-1.40 (m, 4H), 1.53 (d, J = 7.2 Hz, 6H), 1.50 (d, J = 7.2 Hz, 6H), 1.39-1.29 (m 4H), 0.86 (s, 18H), 0.02 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08m, 170.27, 169.97, 68.87, 68.10, 62.94, 62.69, 33.88, 32.44, 25.96, 25.36, 24.60, 18.33, 16.75, 16.72, -5.30; HRMS ($M+NH_4^+$) calc mass 824.4648, found 824.4626.

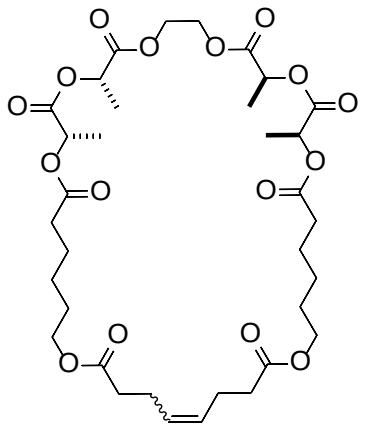


Eg-(LLC)$_2$. To a stirring solution of Eg-(LLC-SiR$_3$)$_2$ (1.48 g, 1.83 mmol, 1 equiv..) in THF (37 mL) under N_2 was slowly added acetic acid (1.7 mL, 29.3 mmol, 16 equiv.) and then tetrabutylammonium fluoride (1.0 M in THF, 5.5 mL, 5.5 mmol at rt. The reaction mixture was poured into brine (50 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (75 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 50-60% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (0.90 g, 84.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (q, J = 7.1 Hz, 2H), 5.08 (q, J = 7.1 Hz, 2H), 4.35-4.28 (m, 4H), 3.61 (t, J = 6.4 Hz, 4H), 2.39 (dt, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 2H), 2.37 (dt, J_1 = 15.6 Hz, J_2 = 7.4 Hz, 2H), 1.70-1.62 (m, 4H), 1.59-1.47 (m, 6H), 1.52 (d, J = 7.2 Hz, 6H), 1.50 (d, J = 7.2 Hz, 6H), 1.44-1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.07, 170.30, 169.95, 68.91, 68.13, 62.66, 62.49, 33.75, 32.21, 25.04, 24.43, 16.71, 16.69; HRMS ($M+H^+$) calc mass 579.2653, found 579.2643.



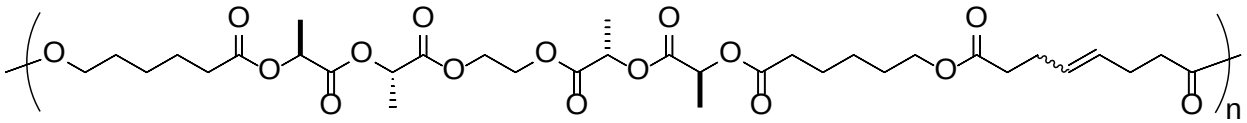
Eg-(LLC-P)$_2$. To a stirring solution of Eg-(LLC)$_2$ (0.65 g, 1.12 mmol, 1 equiv.) and 4-pentenoic acid (0.25 mL, 2.45 mmol, 2.2 equiv.) in CH_2Cl_2 (23 mL) was added DPTS (0.13 g, 0.45 mmol, 0.4 equiv.). Once the mixture became homogeneous, DCC (0.51 g, 2.47 mmol, 2.2 equiv.) was added and the reaction was allowed to stir overnight. The reaction was filtered to remove the urea byproduct, the filtrate was diluted with CH_2Cl_2 (25 mL) and washed with sat. $NaHCO_3$ (50

mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 50 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 15-17.5% EtOAc in hexanes) to provide the product as a colorless liquid (0.77 g, 92.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (m, 2H), 5.13 (q, J = 7.1 Hz, 2H), 5.08 (q, J = 7.2 Hz, 2H), 5.05-5.00 (m, 2H), 4.99-4.96 (m, 2H), 4.36-4.27 (m, 4H), 2.43-2.31 (m, 12H), 1.69-1.58 (m, 4H), 1.52 (d, J = 7.2 Hz, 6H), 1.50 (d, J = 7.2 Hz, 6H), 1.42-1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.04, 172.85, 170.22, 169.92, 136.69, 115.42, 68.85, 68.13, 64.12, 62.67, 33.65, 33.51, 28.85 , 28.27, 25.37, 24.35, 16.71, 16.70; HRMS ($M+H^+$) calc mass 743.34846, found 743.34834.



***cyclic*-Eg-(LLC-P)$_2$**. A solution of Grubbs' 2nd generation catalyst (94.9 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added to a stirring solution of Eg-(LLC-P)$_2$ (0.82 g, 1.11 mmol) in CH_2Cl_2 (815 mL). An additional 1 mL of CH_2Cl_2 was used to rinse the vial that had contained the catalyst solution, and the reaction was allowed to stir at RT overnight. The reaction was quenched by adding 1 mL ethyl vinyl ether, and then concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 15% EtOAc in hexanes) to provide the product as a colorless liquid with an *E/Z* ratio of 7.3/1 (0.58 g, 73.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-

5.39 (*trans*) and 5.37-5.35 (*cis*) (m, 2H), 5.12 (q, J = 7.2 Hz, 2H), 5.08 (q, J = 7.1 Hz, 2H), 4.39-4.25 (m, 4H), 4.05 (*cis*) and 4.04 (*trans*) (t, J = 6.4 Hz, 4H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.07, 172.89, 170.11, 170.02, 129.40 (*trans*), 129.03 (*cis*), 68.93, 68.12, 64.06, 62.64, 34.16, 33.66, 28.26, 27.78, 25.40, 24.38, 16.70 (2); HRMS ($M+H^+$) calc mass 603.19251, found 603.19028.



Poly (CLL-Eg-LLC-Oed)-4. Grubbs' 2nd generation catalyst (0.76 mg, $8.9x10^{-4}$ mmol, 1.33 mol%) was dissolved in CH_2Cl_2 (15 µL), and to a stirring solution of *cyclic*-Eg-$(LC-P)_2$ (48.0 mg, 0.067 mmol) in CH_2Cl_2 (81 µL). The reaction was allowed to stir at RT for 4 h before being quenched through the addition of ethyl vinyl ether was allowed to stir for 5 min and then was dried under vacuum overnight to yield an off-white solid (quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.40 (*trans*) and 5.40-5.35 (*cis*) (m, 2H), 5.13 (q, J = 7.2 Hz, 2H), 5.07 (q, J = 7.2 Hz, 2H), 4.37-4.27 (m, 4H), 4.034 (*cis*) and 4.029 (*trans*) (t, J = 6.8 Hz, 4H), 2.37 (dt, J_1 = 16 Hz , J_2 = 7.6 Hz, 2H), 2.35 (dt, J_1 = 16 Hz, J_2 = 7.4 Hz, 2H), 2.33-2.23 (m, 8H), 1.69-1.58 (m, 8H), 1.53 (d, J = 7,2 Hz, 6H), 1.50 (d, J = 7.2 Hz, 6H), 1.42-1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.09, 172.88, 170.25, 169.93, 129.39 (*trans*), 128.98 (*cis*), 68.85, 68.13, 64.10, 62.69, 34.10, 33.64, 28.27, 27.77, 25.37, 24.35, 16.72, 16.70; DSC: T_g = -11 ^{o}C; SEC (THF): M_n = 47 kDa, M_w = 60 kDa, Đ = 1.3.

Poly (CLL-Eg-LLC-Oed) molecular weight control study. The LLC-macromonomer was added to a vial charged with a stir bar and pumped into a nitrogen filled glove box. An

appropriate amount of dry CH_2Cl_2 (0.7M with respect to monomer final volume) was added to dissolve the monomer. A solution of Grubbs' 2nd generation catalyst (varying catalyst mol %) was prepared and added to monomer solution and allowed to stir for 4h. Monomer, catalyst and solvent amounts can be seen in **Table 9**. After 4h, the polymerizations were quenched with ethyl vinyl ether and allowed to stir for five minutes before concentrating *in vacuo*.

5.0 SYNTHESIS AND PREPARATION OF SEQUENCED PLGA STEREOCOMPLEXES

The work described in this chapter includes synthetic contributions from Michael A. Washington. Some data and polymers were also utilized from the work performed by Ryan M. Stayshich.[15,176]

5.1 INTRODUCTION

5.1.1 Sequence matters

Nature utilizes relatively small libraries of monomers and the sequence of these monomers to give biopolymers such as DNA and peptides numerous functions and properties.[1,2] While nature has had millions of years to perfect the level of sequence control in peptides, synthetic chemists are just now attempting to tackle challenge of sequence control in synthetic polymers.[7,8] Simpler architectures such as alternating, block, and gradient copolymers have been accessed and these materials have displayed properties that vary widely from their random copolymer equivalents.[46-50,177]

Researchers have recently have taken great steps toward the synthesis of materials with an exact sequence.[7,8] Three examples of synthetic methods that have been employed to control

sequence are chain-growth,[51-54,102] step-growth,[15-17,53,55-61] and ring-opening polymerizations.[21,30,104-106] Investigation of the effects that sequence has on monomer properties is an important area of focus to our group. Recently our group has focused on creating sequenced polymers in two areas: conjugated materials[12,13] and poly(α-hydroxy acid)s.[15-20]

5.1.2 Poly(α-hydroxy acid)s and tacticity

Poly(α-hydroxy acid)s such as poly lactic acid (PLA), poly glycolic acid (PGA), and poly caprolactone (PCL), and the copolymer poly(lactic-*co*-glycolic acids) (PLGAs) are biodegradable and bioassimilabile and have been used in drug delivery and tissue engineering scaffolds.[24,26,30] These polymers are usually prepared by ring-opening polymerization of the cyclic compounds lactide, glycolide and ε-caprolactone. When considering PLA, it is important to note that the repeat unit is inherently chiral. Polymers incorporating only L-lactide (*S*-lactide) are generally abbreviated as PLLA, D-lactide (*R*-lactide) as PDLA, and racemic lactide as PLA.

Within PLA or any copolymer that contains lactic units, stereoisomeric relationships are possible. It is common in polymer chemistry to describe these relationships in terms of tacticity, independent of whether the repeat units are inherently chiral as is the case with lactic acid or whether the chirality is introduced only when the units are polymerized, as is the case for propylene.[178] When two neighboring monomers have the same stereochemical orientation they are said to have an isotactic (*i*) relationship, *e.g.*, two *R*-lactic units connected to one another (L_R-L_R). When two neighboring lactic units have opposite stereochemistry (L-L_R), they are said to be syndiotactic (*s*). Homopolymers of one stereoisomer, PLLA or PDLA, are by definition isotactic since the stereochemical relationship between each lactic unit in the polymer is isotactic. In a stereochemically alternating copolymer of PLA (-L-L_R-L-L_R-L-L_R-), each neighboring lactic unit

has opposite stereochemistry (*s*) which gives a fully syndiotactic polymer. When racemic lactide is ring-opened, it yields a stereochemically random copolymer deemed atactic (**Figure 33**).[30] Also important is that stereochemically active units do no not need to be directly connected to be categorized. Hence, a copolymer that includes the stereochemically neutral G unit, such LL_RG could also be considered syndiotactic.

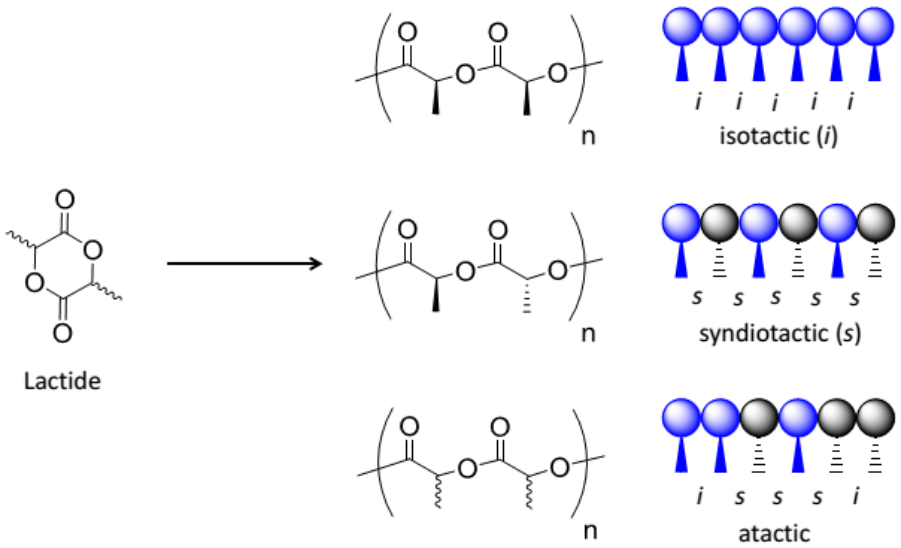


Figure 33. Ring-opening polymerization of lactide to yield varying stereochemical sequences in PLA.

Once polymerized, the stereochemical sequence of the PLA determines the properties of the polymer.[30] For example, the isotactic (*i*) homopolymers PLLA and PDLA have melting transitions between 170-190 °C[179] and syndiotactic PLA (a polymer with an alternating stereosequence, *s*) has a T_m of 152 °C.[180] Random PLA, an amorphous polymer, does not have a melting transition.[30] Stereochemical control in copolymers like PLGA (outside of the polymer by the Meyer Group and described herein) is limited to only isotactic and atactic relationships.[39]

5.1.3 Formation of stereocomplexes

In 1987 Ikada *et al*. reported for the first time the complexation of enantiomeric PLLA and PDLA in solution. This complexation of two different polymers with opposing stereochemistries is called a stereocomplex. The co-precipitates were characterized by DSC and it was observed that the T_m of the polymer mixture had increased to 220-230 °C.[181] The stereocomplex crystals were observed to have a compact 3_1 helical structure (**Figure 34**) where the homopolymers PLLA and PDLA form a 10_3 helix. De Jong *et al*. determined that the minimum lactic unit chain length for the formation of a stereocomplex was 7 while in PLLA/PDLA where a DP ≥ 11 is required for crystallite formation.[182]

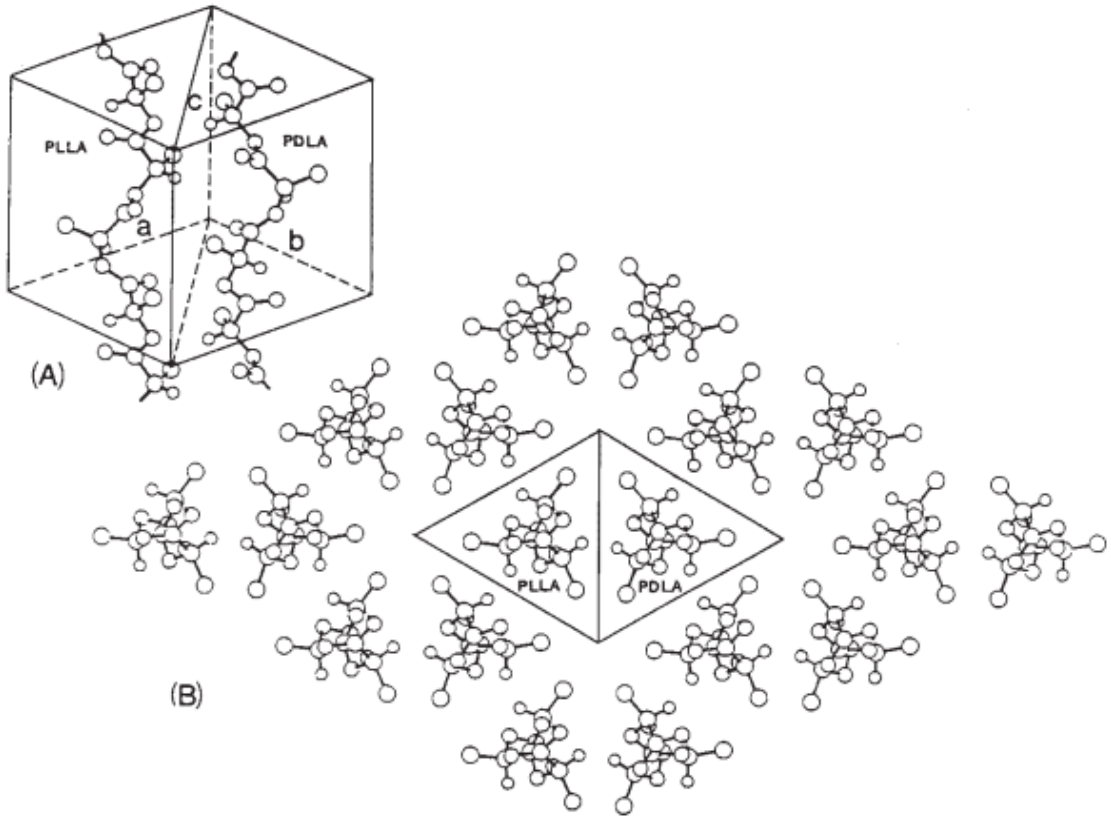


Figure 34. Crystal structure of PLA stereocomplex. *Reprinted with permission from Ref 169, Tsuji, H. "Poly(lactide) stereocomplexes: Formation, structure, properties, degradation, and applications" Macromol. Biosci.* ***2005****, 5, 569. © 2005 John Wiley & Sons, Inc.*

Stereocomplexation in PLA was not the first example of this phenomenon to be observed. In 1953, Pauling and Corey observed the formation of a stereocomplex between L- and D-polypeptides. Complexation of isotactic and syndiotactic poly(methyl methacrylate) was reported by Fox *et al*. in the late 1950s.[183] The first example of a stereocomplex in a polyester was between in poly(α-methyl-α-ethyl-β-propiolactone) between the *R* and *S* isomers.[184] Stereocomplex formation in other poly(α-hydroxy acid) systems include the block copolymer of poly(D-lactide-*b*-L-lactide),[185] poly(L-lactide-*co*-ε-caprolactone) (PLLCA) and poly(D-lactide-*co*-ε-caprolactone) (PDLCA),[186] poly(D-lactide) and poly(L-lactide-*co*-glycolide), poly(D-lactide-*co*-glycolide) and poly (L-lactide-co-glycolide).[187] Stereocomplexation of polymers have seen use in biomedical applications such as formation of hydrogels, drug delivery, gene therapy and tissue engineering scaffolds.[188-191]

The random copolymers PDLGA and PLLGA can also exhibit homo-crystallinity and stereocomplex formation. For homo-crystallization the fraction of lactic units must be greater than 0.75. Stereocomplexes, which form when the two polymers are blended, are observed with polymers that have lower weight fractions of lactic acid, as low as 0.675. The melting transition of the stereocomplex of enantiomeric PLGAs (PDLGA and PLLGA) decreases with the increase of mole fraction of the glycolic unit. In the sample with mole fraction ~0.65 of lactic units a T_m was observed at around 170 °C.[187] The minimum lactic unit sequence length needed to form a stereocomplex in these enantiomeric PLGAs was calculated to be 5.5, lower than the 7 units required for stereocomplex formation in PDLA/PLLA.[184]

5.1.4 Sequenced copolyesters prepared by SAP

Recently, our group has focused heavily on the synthesis of repeating sequenced copolymers of poly(α-hydroxy acid)s such as PLGAs, PLCAs, PGCAs, and PLGCAs. We are interested in the effect that sequence has on polymer properties. The sequenced polyesters are prepared by a step-growth polymerization method in which sequenced oligomers (segmers) are polymerized by utilizing a DIC/DPTS coupling strategy we have deemed Segmer Assembly Polymerization (SAP).[15,17-20] We have found that the melting transitions in sequenced PLGA, PLCA, PGCA, and PLGCAs that the sequence of the monomers and the stereochemical sequence has an effect on copolymer thermal properties.[15,17] In the two PLGCAs that were synthesized, **Poly LGC** and **Poly GLC**, that the order of the monomers grave rise to a difference of almost 10 °C in their T_ms.[17]

5.1.5 Preliminary evidence for the stereocomplex formation in sequenced PLGAs

We became intrigued about the possibility of stereocomplexes in our sequenced PLGAs when we observed an anomaly in the melting temperatures of stereoisomers of polymers with a structural sequence of $(LLG)_n$. We observed that **Poly L$_R$LG** and **Poly LL$_R$G** (154 °C and 154 °C) have alternating lactic unit stereochemistries and have T_ms 40 °C higher than that of the stereopure LLG trimer (114 °C).[15] The syndiotactic sequenced polymers display T_ms that are similar to that of syndiotactic PLA which has a T_m of 152 °C even though the mole fraction of G units is 0.33.[180] Syndiotactic PLA has a lower melting transition than that of the isotactic PLAs.[180] In our system, the syndiotactic LLG sequenced polymers exhibited melting transitions that increased over the isotactic variants. This T_m increase more closely resembles the formation

of a stereocomplex, where two enantiomeric polymers co-crystallize. After observing the unexpected melting transition of the syndiotactic LLG polymer, we set out to explore this unexplained trend.

5.2 RESULTS AND DISCUSSION

5.2.1 Naming conventions

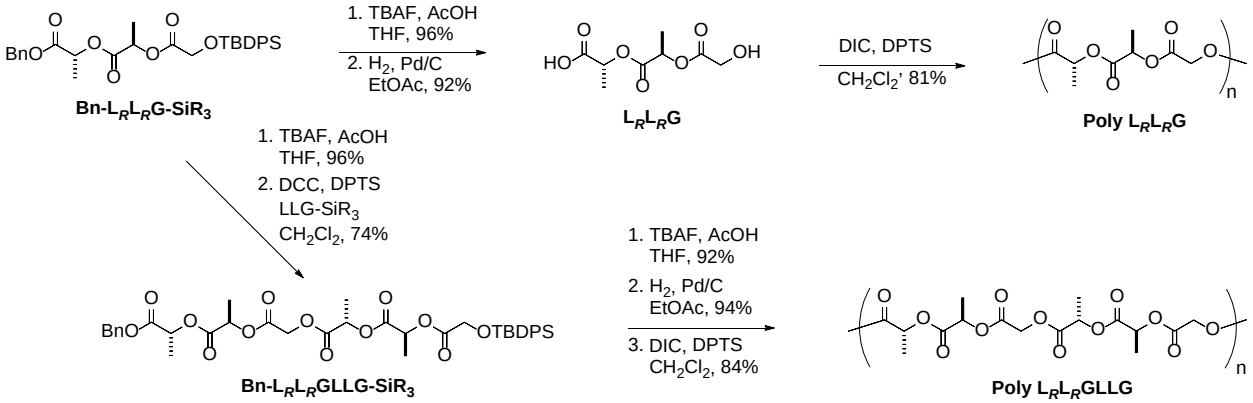
Monomers, segmers (sequenced oligomers), and polymers will be named according to the abbreviations in **Table 10**. Orthogonally protected monomers of L-lactic acid (L), D-lactic acid (L_R), and glycolic acid (G) units were prepared according to previous literature.[15,17,21,59,176] Segmers are listed in order by sequence from the carboxylic acid end to the alcohol terminus. Using these naming conventions, the compound with the name of **Bn-L_RL_RG-SiR_3** is a trimer that is composed of a benzyl protected *R*-lactic acid unit, an *R*-lactic acid unit, and a *tert*-butyldiphenylsilyl protected glycolic acid unit. Once the trimer has been deprotected, the segmer is polymerized, and the obtained polymer is given the name from the segmer from which it was synthesized, i.e. **Poly L_RL_RG**. The polymer consists of the repeating sequence of L_RL_RG or ...$L_RL_RGL_RL_RGL_RL_RGL_RL_RGL_RL_RGL_RL_RG$...

Table 10. Naming conventions for the segmers and polymers

Symbol	Definition
L	L-Lactic acid unit (*S* stereocenter)
L_R	D-Lactic acid unit (*R* stereocenter)
G	Glycolic acid unit
Bn	Benzyl protecting group
SiR_3	Silyl protecting group (*tert*-butyldiphenylsilyl)

5.2.2 Synthesis and characterization of repeating sequence copolymers towards the creation of copolymer stereocomplexes

Starting with the orthogonally mono-protected acids (**Bn-L**, **Bn-L$_R$**, and **Bn-G**) and alcohols (**L-SiR$_3$**, **L$_R$-SiR$_3$**, and **G-SiR$_3$**), dimers were formed via the Steglich esterification reaction using DCC/DPTS.[15,17,21,59,82,176] The silyl group was then removed from the dimer **Bn-L$_R$L$_R$-SiR$_3$** using TBAF/AcOH to yield the protected acid **Bn-L$_R$L$_R$** (**Scheme 12**). Coupling the free alcohol with **L$_R$-SiR$_3$** gave the doubly protected trimer of **Bn-L$_R$L$_R$G-SiR$_3$**. Silyl deprotection followed by hydrogenolysis reaction over Pd/C to the benzyl protecting group, produced the unprotected trimer **L$_R$L$_R$G**. The polymer **Poly L$_R$L$_R$G** was synthesized by a step-growth polymerization in the presence of DIC/DPTS. It is well established that these reaction conditions do not promote sequence-scrambling transesterification. Longer segmers, such as **Bn-L$_R$L$_R$GLLG-SiR$_3$** were prepared by coupling of shorter segmers that had been partially deprotected, e.g., **Bn-L$_R$L$_R$G** and **LLG-SiR$_3$**. These longer segmers could then be doubly deprotected and polymerized as described to give a polymer such **Poly L$_R$L$_R$GLLG** which we categorize as "mini-block" copolymers herein.



Scheme 12. Overall scheme towards the synthesis of repeating sequence copolymers **Poly L$_R$L$_R$G** and **Poly L$_R$L$_R$GLLG** beginning with the trimer **Bn-L$_R$L$_R$G-SiR$_3$**.

The polymers were synthesized in good yield, ranging from 46-86% (**Table 11**). The molecular weights of the polymers were determined by SEC in THF relative to PS standards. The M_ns ranged generally from 17-41 kDa, with the exception of **Poly LLLLG** and **Poly $L_RL_RL_RL_RG$**. The pentamers of these two polymers were highly crystalline and were difficult to dissolve for the polymerization and a 1:1 DMF/CH_2Cl_2 solvent mixture needed to be utilized. The catalyst DPTS, however, has a low solubility in DMF and we hypothesize that the low M_ns obtained for these two polymers (6.0 and 8.8 kDa) is due to these solubility issues.

Table 11. Polymer molecular weight and melting transition data

Polymer	Yield (%)	M_n (kDa)[a]	M_w (kDa)[a]	Đ[b]	Anneal temp (°C)[c]	T_g (°C)[d]	T_m (°C)[e]
Poly LG	63	33.4	39.5	1.2	100	55	107
Poly L_RG	46	23.0	32.0	1.4	100	53	107
Poly LLG	70	41.2	50.5	1.2	100	50	114
Poly L_RL_RG	81	26.2	38.4	1.5	100	53	117
Poly LL_RG	75	30.3	40.3	1.3	85	49	154
Poly L_RLG	59	30.6	43.1	1.4	85	50	154
Poly GLLG	82	18.7	25.1	1.3	85	45[e]	---
Poly L_RL_RGG	76	25.1	35.3	1.4	85	nd	---
Poly LLLG	86	20.8	31.1	1.5	85	52[e]	---
Poly $L_RL_RL_R$G	81	31.9	43.2	1.4	85	55	---
Poly LLLLG	82	8.8	12.1	1.6	85	52	160
Poly $L_RL_RL_RL_R$G	83	6.0	7.8	1.3	85	53	154
Poly L_RL_RGLLG	84	17.1	25.3	1.5	85	50	98 (132)[f]
Poly $L_RL_RL_R$GLLLG	74	23.9	30.8	1.3	85	55	99 (124)[f]
Poly $L_RL_RL_RL_R$GLLLLG	83	37.8	46.9	1.2	145	57	---

a) Determined by SEC in THF relative to PS standards. b) M_w/M_n. c) Annealed for 3h d) Obtained in the 2nd heating cycle at 10°C/min e) Obtained in the 1st heating cycle at 10°C/min f) 2nd melting transition.

Of the polymers prepared, the majority are isotactic (*i*): **poly LG**, **LLG**, **GLLG**, **LLLG**, **LLLLG**, and their enantiomers. **Poly LL_RG** and **Poly L_RLG**, are stereochemically syndiotactic (*s*). The "mini-block" polymers, **Poly L_RL_RGLLG**, **Poly $L_RL_RL_RGLLLG$**, and **Poly $L_RL_RL_RL_RGLLLLG$,** have more complex tacticities, *is*, *iis*, and *iiis*, respectively. Note: the tacticity in this case refers only to the relative stereochemistries of neighboring, but not necessarily adjacent, units. Thus, the tacticity of **Poly L_RL_RGLLG**, whose chain sequence once expanded to include multiple repeat units becomes **-$L_RL_RGLLGL_RL_RGLLGL_RL_RGLLG$-** can

be described concisely as *is* by simple reference to the relative stereochemistries (*i*) of the adjacent L units followed by the relative stereochemistry of the L units that are separated by Gs (*s*) (**Figure 35**).

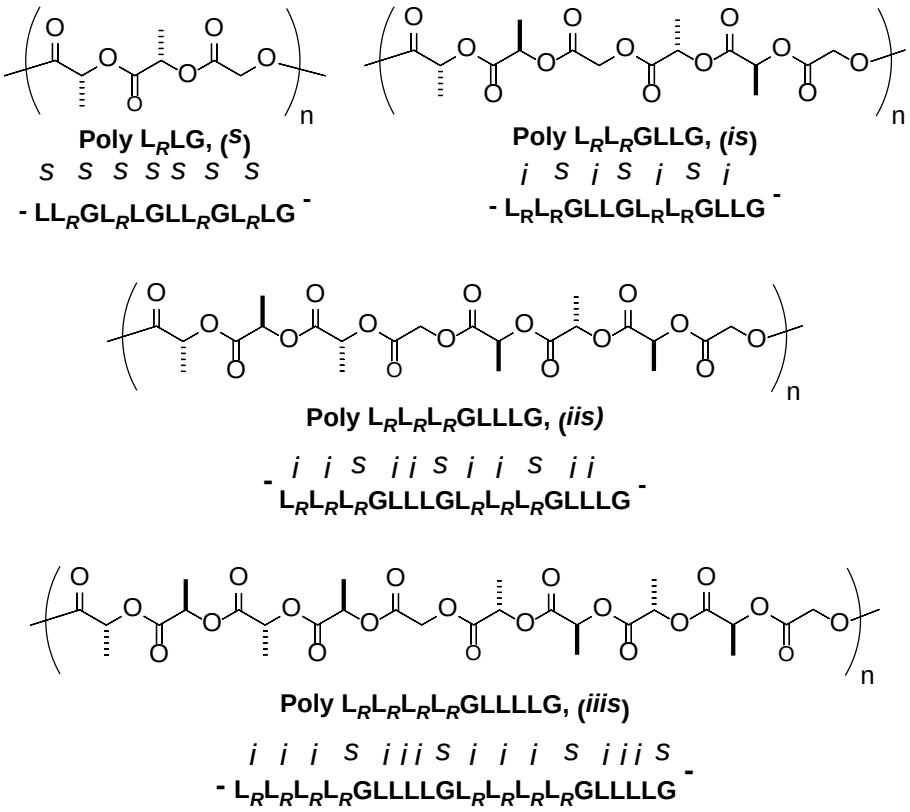


Figure 35. The four mini-blocks that were synthesized by SAP. Below each polymer is the tacticity assignment of the polymer: **Poly L$_R$LG** (*s*), **Poly L$_R$L$_R$GLLG** (*is*), **Poly L$_R$L$_R$L$_R$GLLLG** (*iis*), and **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** (*iiis*).

5.2.3 Characterization of isotactic and mini-block sequenced copolymers by ^{1}H NMR spectroscopy

The sequenced polymers were characterized by ^{1}H NMR spectroscopy. The Meyer group has demonstrated previously that chemical shift of the diastereotopic glycolic methylene protons are extremely sensitive to monomer sequence, particularly stereosequence.[15] This trend continues for the new copolymers prepared for the purposes of this study. For example, there are significant

differences between the NMR spectra of segmer **L$_R$L$_R$L$_R$L$_R$GLLLLG** and **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** (**Figure 36**). Once polymerized, all of the methylene units become equivalent—since all are located between L units of opposite stereochemistry.

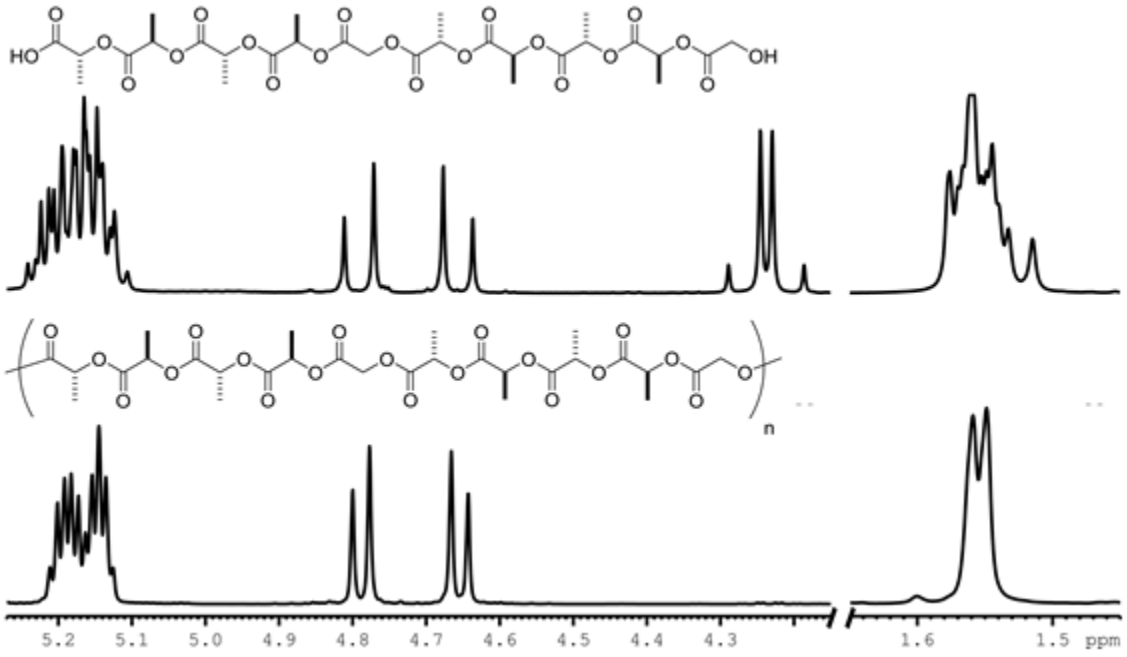


Figure 36. Comparison between the ^{1}H NMR spectra of **L$_R$L$_R$L$_R$L$_R$GLLLLG** (top, 400 MHz) and **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** (bottom, 700 MHz).

The NMR data for the mini-block copolymers **Poly L$_R$LG**, **Polys L$_R$L$_R$GLLG**, **L$_R$L$_R$L$_R$GLLLG**, and **L$_R$L$_R$L$_R$L$_R$GLLLLG** are shown in **Figure 37**. In this case, the G unit chemical shift is relatively unaffected by the addition of L units beyond the second. The addition of L units is primarily observed in the increase in number of signals and integration for the L methine and methyl groups.

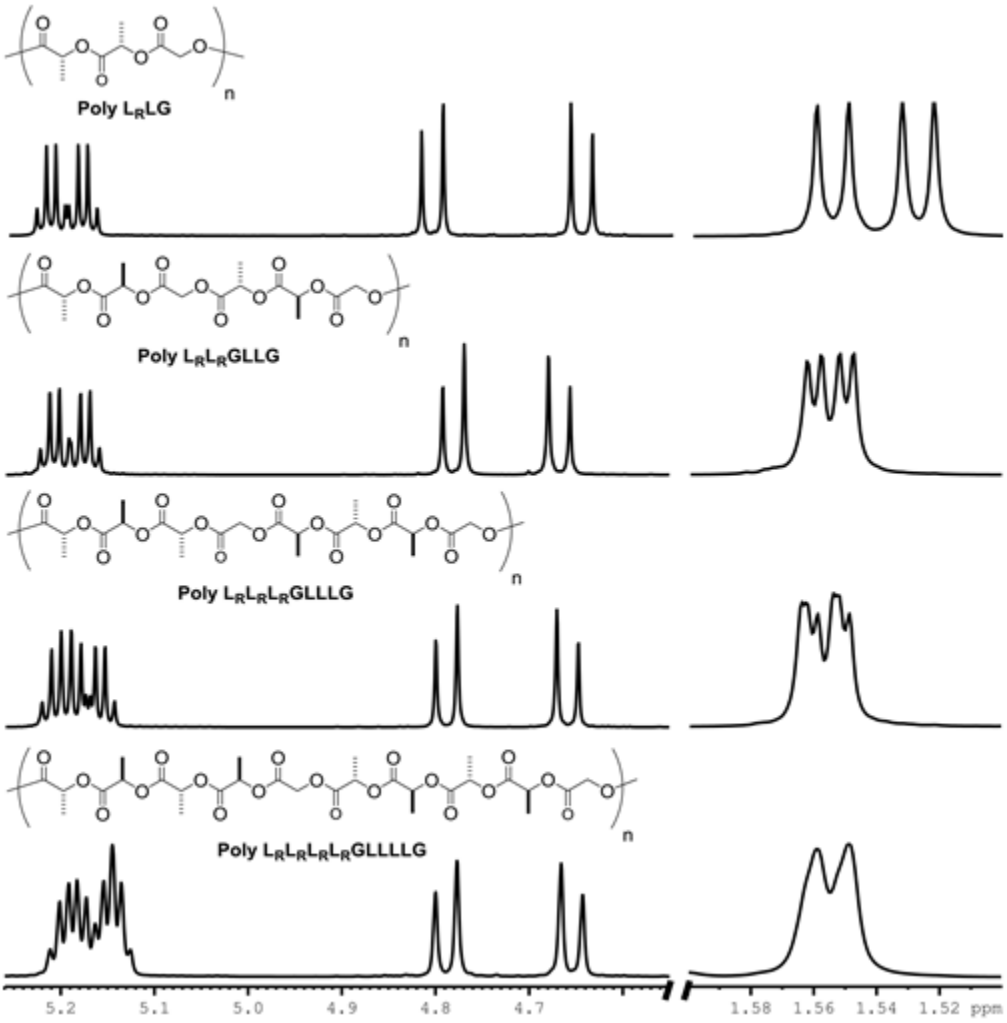


Figure 37. Comparison between the ^{1}H NMR spectra (700 MHz) of **Poly L$_R$LG** (top), **Poly L$_R$L$_R$GLLG** (top middle), **Poly L$_R$L$_R$L$_R$GLLLG** (bottom middle) and **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** (bottom).

The stereochemistry around the G unit, in contrast, has a significant effect on the diastereotopic G methylene chemical shifts when comparing a fully isotactic copolymer and the mini-block equivalent. When comparing the ^{1}H NMR spectra of **Poly L$_R$L$_R$L$_R$G** and **Poly L$_R$L$_R$L$_R$GLLLG**, the isotactic polymer (*i*) exhibits a significant difference in the chemical shifts of the diastereotopic methylene resonance when compared to the *iis* copolymer (**Figure 38**). The magnitude of the difference makes it possible for us to unambiguously differentiate between these copolymers despite their structural homology.

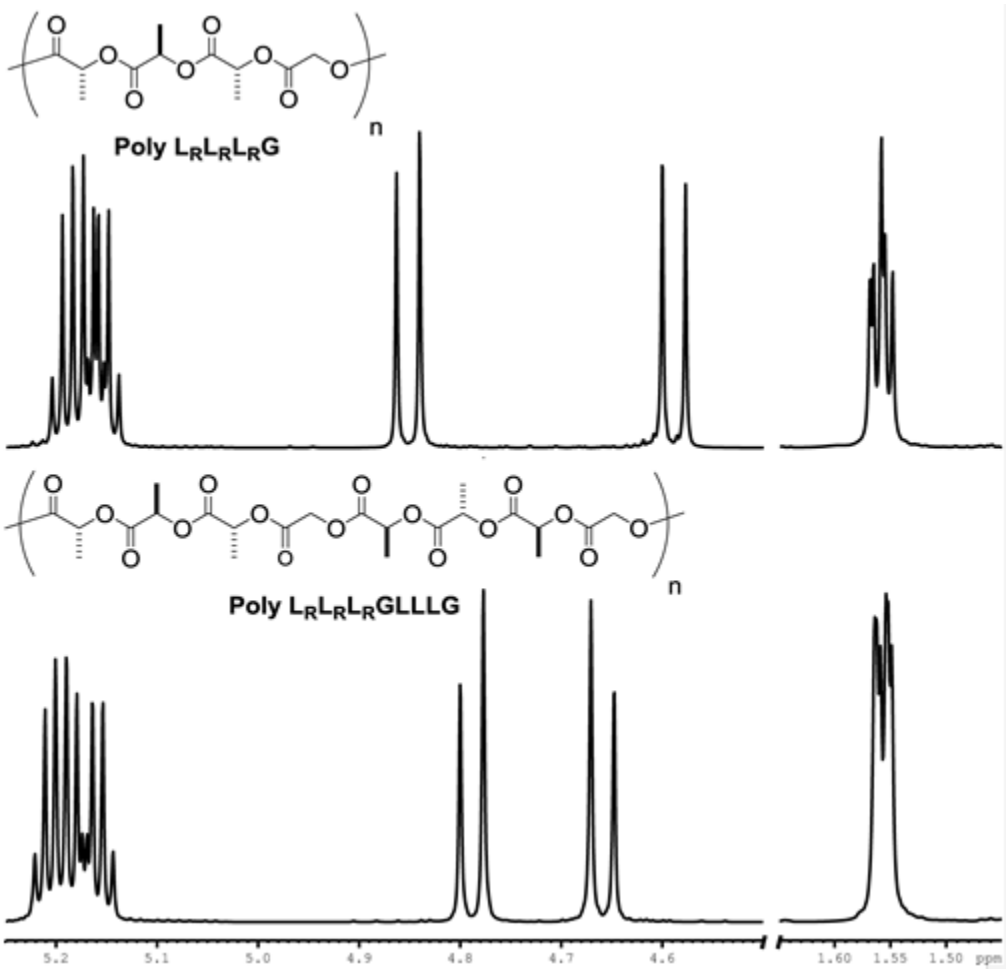


Figure 38. Comparison of the ^{1}H NMR (700 MHz) spectra of **Poly $L_RL_RL_RG$** and **Poly $L_RL_RL_RGLLLG$**.

The most important aspect of the NMR data of these compounds, one that cannot be overemphasized, is that we can use the data to unambiguously confirm that the sequence created in the segmers is preserved in the polymer and that the polymers studied are free of significant sequence errors.

5.2.4 Characterization of sequenced PLGA copolymers by differential scanning calorimetry

The sequenced polymers were characterized by DSC to determine their melting transitions. The polymers were annealed at 85 or 100 °C in aluminum DSC pans for 3 h. The samples were heated at 10 °C/min and the T_ms were obtained in the first heating cycle (**Table 11**). **Poly LG** and **Poly L$_R$G** exhibited melting transitions at 107 °C, while **Poly LLG** and **Poly L$_R$L$_R$G** had T_ms observed at 114 °C. The pentamers **Poly LLLLG** and **Poly L$_R$L$_R$L$_R$L$_R$G** displayed T_ms at 160 and 154 °C respectively. As the L unit mole fraction was increased from 0.5 to 0.8 the melting transition increased. The isotactic copolymers **Poly GLLG** and **Poly LLLG** and the mini-block **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** did not exhibit melting transitions under the annealing conditions used. This is especially surprising for **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG**, where the L unit mole fraction is 0.8.

5.2.5 Stereocomplex formation of sequenced PLGAs

We set out to form stereocomplexes of our sequenced PLGAs by either mixing the enantiomeric copolymers (i.e. combining **Poly LLG** and **Poly L$_R$L$_R$G**) or investigating the polymers that contained mini-blocks of lactic units (i.e. **Poly L$_R$L$_R$GLLG)**. For the enantiomeric blends, the individual polymers (for example **Poly LLG** and **Poly L$_R$L$_R$G**, 1:1 weight fraction) were each dissolved in dry CH_2Cl_2 (2.5 mL) to obtain a concentration of 1 g/dL. The two solutions were then combined and vortexed. The copolymer solution was precipitated into rapidly stirring methanol (500 mL) and allowed to stir for 30 min before filtering the precipitation solution through a nylon filter to collect the coprecipitated enantiomeric blend as powders.[192] The

polymers containing mini L blocks were prepared similarly to the blends; however, they were not mixed with another polymer.

The coprecipitated polymer blends and mini-block copolymers were then annealed at temperatures ranging from 85-176 °C depending on the polymer blend. The annealed samples were then characterized by DSC to determine if stereocomplexes had been formed based on comparing the T_ms of the polymer blends to that of the nonblended polymers (**Table 12**). **Poly LLG** and **Poly L_RL_RG** both have T_ms of ~114 °C when annealed at 85 °C (**Figure 39**). When annealed at 130 ºC a melting transition is no longer observed. Once blended and annealed at 130ºC a new melting transition is found at 147 °C giving strong evidence that a stereocomplex had indeed formed. Another example of a stereocomplex that was formed was the **Poly LG/L_RG** blend. Annealing the blend at 130 °C yields a T_m at 144 °C, however, the transition is much weaker than that of the LLG blend.

Table 12. Melting transitions of polymer stereo blends

Polymer blend	T_m (°C) of non-blended polymer	Annealing temperature of blend (°C)[c]	Stereocomplex T_m (°C)[d]
LG/L_RG	107, 107[a]	130	144
LLG/L_RL_RG	114, 117[a]	130	147
LL_RG/L_RLG	154,154[b]	156	159
GLLG/L_RL_RGG	---	130	---
LLLG/$L_RL_RL_R$G	---	145	---
LLLLG/$L_RL_RL_RL_R$G	160, 154[b]	176	---
L_RL_RGLLG	---	145	143
$L_RL_RL_R$GLLLG	---	145	151
$L_RL_RL_RL_R$GLLLLG	---	145	---

a) Annealed at 100 °C b) Annealed at 85 °C c) Samples were annealed overnight in an aluminum DSC pan d) T_ms were obtained in the 1st heating cycle, 10 °C/min.

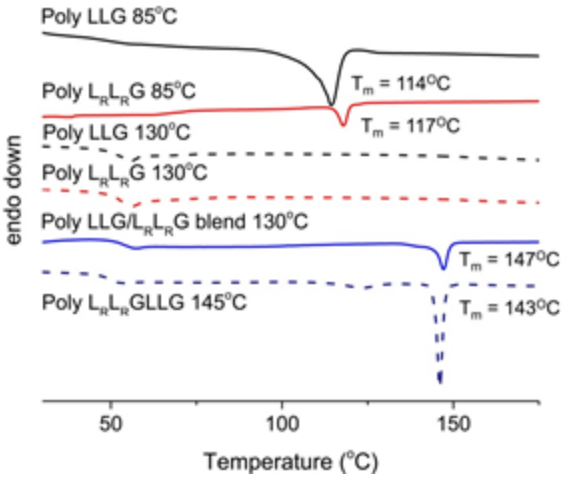


Figure 39. DSC of **Poly LLG** annealed at 85 (black solid line) and 130 °C (black dashed line), **Poly L$_R$L$_R$G** annealed at 85 (red solid line) and 130 °C (red dashed line), **Poly LLG/L$_R$L$_R$G** blend annealed at 130 °C (blue solid line), and **Poly L$_R$L$_R$GLLG** annealed at 145 °C (blue dashed line). Stereocomplexes indicated to have formed in the LLG blend and **Poly L$_R$L$_R$GLLG** where the T$_m$s of the polymers have been raised from ~114 to ~143 °C.

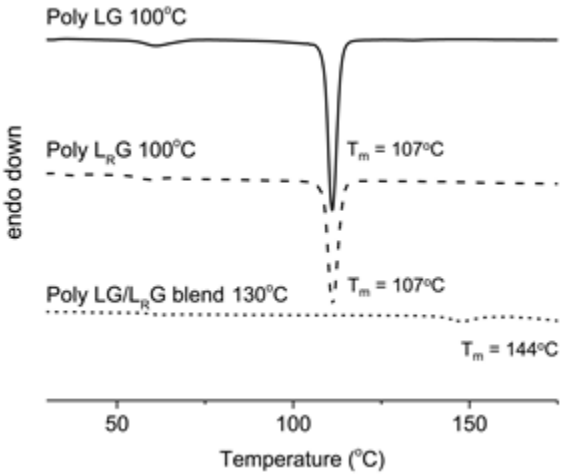


Figure 40. DSC of **Poly LG** annealed at 100 °C (solid line), **Poly L$_R$G** annealed at 100 °C (long dashed line), and **Poly LG/L$_R$G** blend annealed at 130 °C (short dashed line). A stereocomplex melting transition is indicated to have formed due to the increased T$_m$ observed in the **Poly LG/L$_R$G blend** (144 °C).

Interestingly, varying the annealing temperature of the blends and the mini-blocks had a dramatic effect on the T$_m$s of the polymers. An example of this can be seen in the **Poly LLG/L$_R$L$_R$G** blend and in **Poly L$_R$L$_R$GLLG** (**Figure 41**). In the **Poly LLG/L$_R$L$_R$G** blend, annealing below the T$_m$s of the individual polymers (~114 °C) yields a melting transition that resembles the non-blended polymers. Annealing above 114 °C at 145 °C yields a T$_m$ of 145 °C, a 30 °C increase indicating that a stereocomplex had formed for the **Poly LLG** blend. In the **Poly**

L$_R$L$_R$GLLG sample, annealing below 120 ^oC gives two broad melting transitions. T_ms between 99-110 ^oC (when annealed at 85 and 100 ^oC respectively) are suspected to be that of the homocrystallites. Annealing at 145 ^oC, one strong melting transition is observed at 143 ^oC, which is very similar to the stereocomplex T_m of the **Poly LLG** blend.

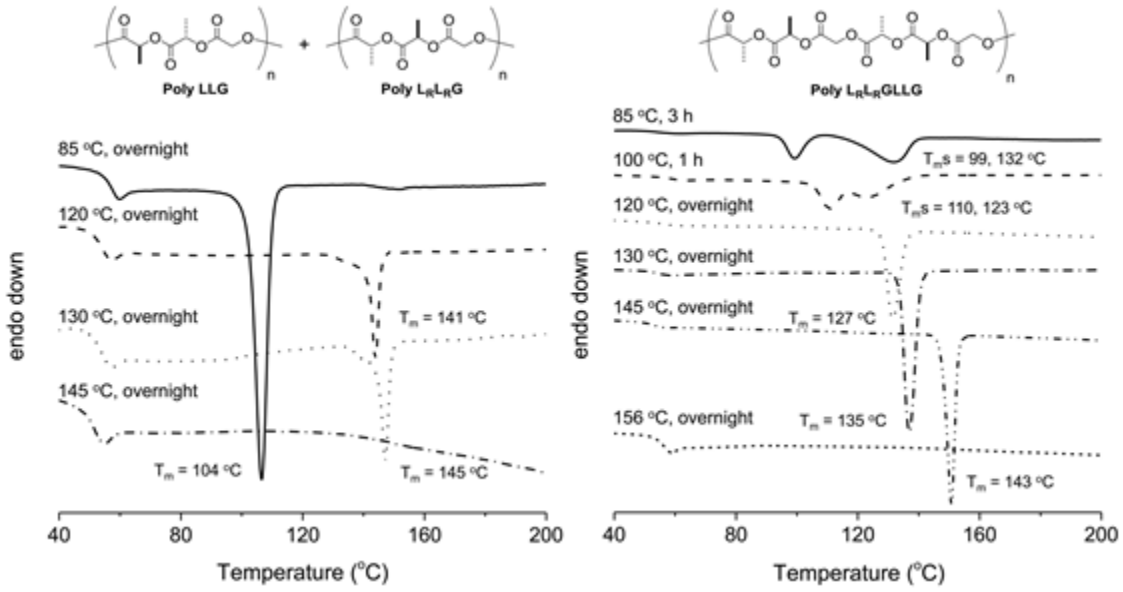


Figure 41. The effect of increasing the annealing temperature from 85-145 °C on the **Poly LLG/L$_R$L$_R$G** blend (left) and 85-156 °C for **Poly L$_R$L$_R$GLLG**.

We have observed evidence of stereocomplex formation in two different sequenced enantiomeric blends **Poly LG/L$_R$G** and **Poly LLG/L$_R$L$_R$G** and two of the sequenced mini-blocks **Poly L$_R$L$_R$GLLG** and **Poly L$_R$L$_R$L$_R$GLLLG**. After annealing the polymer blends at temperatures greater than the T_ms of the non-blended polymers, T_ms of 33-37 ^oC higher were observed. These raised melting temperatures are initial evidence that stereocomplexes have formed between our sequenced PLGAs. Mini-block copolymers that contain opposing stereochemical blocks were found to have melting transitions between 143-151 ^oC after they were annealed. These melting transitions are similar to the T_ms of the sequenced blends of the same lactic unit content. In the mini-block **Poly L$_R$L$_R$L$_R$GLLLG** a stereocomplex was formed as

evidenced by the T_m at 151 °C, but a stereocomplex of the similar **Poly LLLG/L$_R$L$_R$L$_R$G** blend was not formed. This is surprising since all of the other enantiomeric blends that exhibited a stereocomplex T_m, displayed nearly identical transitions in their mini-block equivalents.

It was not obvious why stereocomplexes were not observed for blends based on **Poly GLLG** and **Poly LLLG** nor for the mini-block copolymer **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG.** It is possible that these sequences are somehow poorly suited to forming polymer crystals. There may be some level of "geometric frustration" which inhibits the formation of local crystallites.[193] A particular sequence may not, for example, have a place where a lamellar "turn" will allow for the perfect registry of one section of the copolymer with another. Future modeling experiments of the folding and helical nature of these polymers may prove to be useful in predicting crystallinity in sequenced PLGAs.

We did attempt to acquire both powder x-ray diffraction (XRD) in collaboration with researchers from the research group of Prof. Nat Rosi and wide-angle X-ray scattering (WAXS) in collaboration with researchers from the group of Prof. Tomasz Kowalewski of CMU on some of the materials that exhibited melting points. In both cases it proved difficult to prepare samples with sufficient crystallinity in the format required. In the case of XRD, for example, we were unable to obtain a fine-enough powder despite many attempts.

5.3 CONCLUSIONS

Sequenced PLGA isotactic polymers and stereochemical mini-block copolymers with increasing L unit content were synthesized and characterized by ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra it was found that the peaks were well resolved for all of the polymers synthesized.

Isotactic sequenced copolymers such as **Poly $L_RL_RL_RG$** (*iii*) could be distinguished from the stereoblock isomer, **Poly $L_RL_RL_RGLLLG$** (*iis*) through analysis of the G methylene resonances which are particularly sensitive to the surrounding stereochemical and monomeric sequence.

Characterization of the individual copolymers by DSC showed that as the lactic unit content increased in the copolymers, the T_ms of the polymers increased. This trend matched that of PLGAs synthesized with 0.75 lactic acid content and above in the literature.[187] The mini-block copolymers when annealed below 120 ^oC exhibited melting transitions for the homocrystallites as well for the stereocomplexes.

Upon blending enantiomeric mixtures of polymers (*i.e.* **Poly LLG** and **Poly L_RL_RG**) and annealing them at temperatures greater than the T_ms of the non-blended polymers, T_ms of 33-37 ^oC higher were observed. These raised melting temperatures are initial evidence that stereocomplexes have formed between our sequenced PLGAs. Mini-block copolymers that contain opposing stereochemical blocks were found to have melting transitions between 143-151 ^oC after they were annealed. These melting transitions are similar to the T_ms of the sequenced blends of the same lactic unit content.

5.4 FUTURE WORK

In future experiments, the polymers **Poly GLLG** and **Poly LLLG** and the mini-block **Poly $L_RL_RL_RL_RGLLLLG$** should be subjected to a wider range of annealing conditions to try and form polymer crystallites, e.g., increased annealing time and varied annealing temperatures. Another experiment that could be performed is preparing the blends from the melt instead of the

coprecipitation method that was utilized in this study. Preparing the stereocomplexes from the melt has been used in the literature previously.[184] Finally, it may also be possible to induce crystallization by seeding or through the introduction of external stress during annealing.

While the data suggests that stereocomplexes of the polymers in this study are forming based on the data obtained DSC, the formation of a stereocomplex needs to be confirmed by another method such as XRD or WAXS. WAXS and small-angle X-ray scattering were used previously to characterize the crystal structure of PLA stereocomplexes.[184] To obtain these data, it will likely be necessary to collaborate more closely with groups who have experience with similar materials and can, therefore, provide advice regarding the sample preparation in addition to helping with the collection and analysis of data.

5.5 EXPERIMENTAL

5.5.1 General information

All experiments were carried out in oven-dried glassware under an atmosphere of N_2 using standard Schlenk line techniques. N,N'-dicyclohexylcarbodiimide (DCC) was purchased from Oakwood Chemical and used without further purification. 10% Pd/C was purchased from Alfa Aesar. Methylene chloride (CH_2Cl_2, Fisher) and ethyl acetate (EtOAc, Sigma Aldrich) were purified by a Solvent Dispensing System by J. C. Meyer. Both were passed over two columns of neutral alumina. Anhydrous, inhibitor-free Tetrahydrofuran (THF, $\geq$99.9%) was purchased from EMD and passed over activated alumina. Column chromatography was performed using Sorbent Technologies 60 Å, 40-63 μm standard grade silica. 4-(dimethylamino)pyridinium 4-

toluenesulfonate (DPTS),[82] **Bn-G**, **Bn-L**, **Bn-L$_R$**, **L-SiR$_3$**, **L$_R$-SiR$_3$**, **Bn-GG-SiR$_3$**, **Bn-LL-SiR$_3$**, **Bn-LLG-SiR$_3$**, **Bn-LLLG-SiR$_3$**, **Bn-LLLG**, **LLLG**, **Poly LLG, Poly L$_R$LG**, **Poly LL$_R$G**, and **Poly LLLG** were prepared according to previously-published protocols.[15,59,176] All other chemicals were used without further purification.

5.5.2 Characterization of synthesized compounds

NMR spectroscopy. ^{1}H (300, 400, 500, 600, and 700 MHz) and ^{13}C (75, 100, 125, 150, and 175 MHz) spectra were obtained using Bruker spectrometers and are reported as δ values in ppm relative to the reported solvent ($CDCl_3$ referenced to 7.24). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and combinations thereof.

Mass spectrometry. HRMS data were obtained on a LC/Q-TOF instrument.

Size exclusion chromatography. Molecular weights and dispersities were obtained on a Waters GPC (THF) with Jordi 500, 1000, and 10000 Å divinyl benzene columns, and refractive index detector (Waters) was calibrated to polystyrene standards. For poly L_RL_RGG and poly L_RG SEC data was obtained on a Waters Instrument equipped with a 717 plus autosampler, a Waters 2414 refractive index (RI) detector and two SDV columns (Porosity 1000 and 100000 Å; Polymer Standard. The eluent was THF (1 mL/min, 40 ^{o}C) and the molecular weights were calibrated to PS standards.

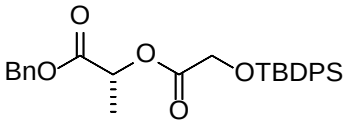
Services)

Differential scanning calorimetry. DSC was performed with a TA Instruments Q200. Samples were prepared by first dissolving in CH_2Cl_2, dropcast into aluminum pans, and put under vacuum

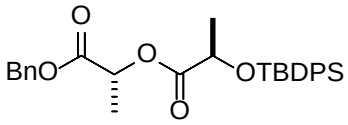
overnight. The samples were then annealed at 85 ^{o}C for 3 h. Each run had a heating and cooling rate of 10 ^{o}C/min. T_gs were collected in the in the first heating cycle.

5.5.3 Synthesis of sequenced PLGAs for stereocomplex formation

5.5.3.1 DCC/DPTS coupling reactions

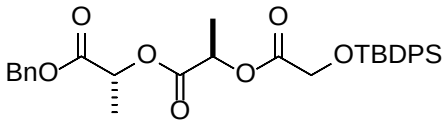


Bn-L$_R$G-SiR$_3$. To a stirring solution of Bn-L$_R$ (2.71 g, 15.0 mmol) and G-SiR$_3$ (5.21 g, 16.6 mmol), in CH_2Cl_2 (150 mL) was added DPTS (0.91 g, 3.1 mmol). Once the mixture became homogeneous, DCC (3.43 g, 16.6 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (5.71 g, 79.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69- 7.65 (m, 4H), 7.44-7.29 (m, 11H), 5.19-5.12 (m, 3H), 4.35 (d, J = 16.4 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58, 170.26, 135.57, 135.54, 135.26, 134.77, 132.70, 132.69, 129.88, 129.62, 128.58, 128.37, 128.37, 128.08, 127.79, 127.77, 127.69, 68.73, 67.00, 61.99, 26.61, 19.25, 16.86; HRMS ($M+NH_4^+$) calc mass 494.23573, found 494.23094.

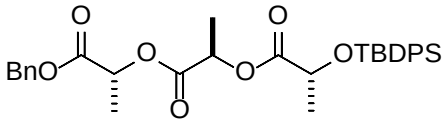


Bn-L$_R$L$_R$-SiR$_3$. To a stirring solution of Bn-L$_R$ (15.0 g, 83.0 mmol) and L$_R$-SiR$_3$ (30.0 g, 91.3 mmol), in CH_2Cl_2 (830 mL) was added DPTS (4.91 g, 16.7 mmol). Once the mixture became

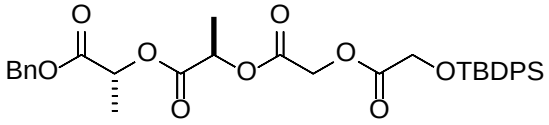
homogeneous, DCC (18.8 g, 91.1 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (39.9 g, 98.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.61 (m, 4H), 7.44-7.27 (m, 11H), 5.14 (d, J = 12.0 Hz, 1H), 5.08 (d, J = 12.0 Hz, 1H), 4.97 (q, J = 7.1 Hz, 1H), 4.30 (q, J = 6.8 Hz, 1H), 1.36 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.04, 170.30, 135.94, 135.74, 135.23, 133.45, 133.07, 129.76, 128.55, 128.38, 128.18, 127.62, 127.54, 68.52, 66.96, 60.37, 26.77, 21.06, 19.20, 16.71; HRMS ($M+Na^+$) calc mass 513.2073, found 513.2063.



Bn-L*R*L*R*G-SiR3. To a stirring solution of Bn-L*R*L*R* (5.00 g, 19.8 mmol) and G-SiR_3 (6.87 g, 21.8 mmol), in CH_2Cl_2 (200 mL) was added DPTS (1.22 g, 4.15 mmol). Once the mixture became homogeneous, DCC (4.6 g, 22 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (8.17 g, 75.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.44-7.28 (m, 11H), 5.19 (q, J = 7.1 Hz, 1H), 5.17 (d, J = 12.8 Hz, 1H), 5.12 (d, J = 12.8 Hz, 1H), 5.11 (q, J = 7.1 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.60, 170.04, 169.84, 135.57, 135.54, 135.11, 134.78, 132.73, 132.70, 129.88, 128.60, 128.48, 128.22, 127.80, 127.78, 69.13, 68.44, 67.15, 61.96, 26.61, 19.25, 16.76, 16.66; HRMS ($M+Na^+$) calc mass 571.2128, found 571.2139.

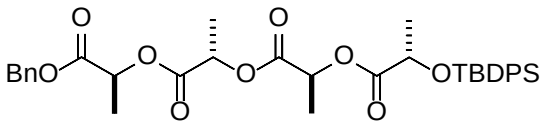


Bn-L*R*L*R*L*R*-SiR3. To a stirring solution of Bn-L*R*L*R* (1.82 g, 7.21 mmol) and L*R*-SiR3 (2.61 g, 7.94 mmol), in CH_2Cl_2 (70 mL) was added DPTS (0.42 g, 1.44 mmol). Once the mixture became homogeneous, DCC (1.66 g, 8.04 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (14.23 g, 88.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.44-7.28 (m, 11H), 5.16 (d, J = 12.0 Hz, 1H), 5.15 (q, J = 7.1 Hz, 1H), 4.32 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.32 (d, J = 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.10, 170.04, 169.88, 135.95, 135.75, 135.12, 133.44, 133.07, 129.78, 129.76, 128.59, 128.46, 128.22, 127.64, 127.56, 69.06, 68.49, 68.25, 67.12, 26.78, 21.12, 19.20, 16.75, 16.50; HRMS ($M+Na^+$) calc mass 585.2285, found 585.2303.

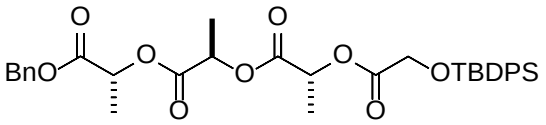


Bn-L*R*L*R*GG-SiR3. To a stirring solution of Bn-L*R*L*R* (3.18 g, 12.6 mmol) and GG-SiR3 (5.18 g, 13.9 mmol), in CH_2Cl_2 (125 mL) was added DPTS (0.74 g, 2.5 mmol). Once the mixture became homogeneous, DCC (2.88 g, 13.4 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to provide the product as a colorless liquid (7.02 g, 91.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.44-7.29 (m, 11H), 5.19 (q, J = 7.2 H, 1H), 5.18 (q, J = 7.2 H, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.12 (d,

J = 12.4 Hz, 1H), 4.74 (d, J = 16.4 Hz, 1H), 4.63 (d, J = 16.0 Hz, 1H), 4.36 (d, J = 17.2 Hz, 1H), 4.32 (d, J = 16.8 Hz, 1H), 1.51 (d, J = 7.6 Hz, 3H), 1.49 (d, J = 7.6 Hz, 3H), 1.07, (s, 9h); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 169.60, 169.45, 166.87, 135.53, 135.05, 132.60, 132.58, 129.91, 128.60, 128.49, 128.22, 127.80, 69.27, 69.08, 61.81, 26.59, 19.23, 16.73, 16.60; HRMS (M-C$(CH_3)_3$) calc mass 549.1581, found 549.1585.

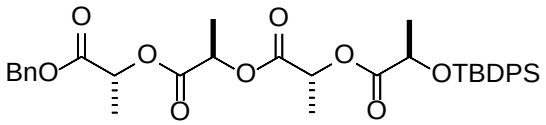


Bn-LLLL-SiR$_3$. Prepared by Michael A. Washington. To a stirring solution of Bn-LL (1.29 g, 5.11 mmol) and LL-SiR_3 (1.89 g, 4.72 mmol), in CH_2Cl_2 (50 mL) was added DPTS (0.28 g, 0.97 mmol). Once the mixture became homogeneous, DCC (1.18 g, 5.73 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5-7.5% EtOAc in hexanes) to provide the product as a colorless liquid (2.70 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ .68-7.64 (m, 4H), 7.42-7.28 (m, 11H), 5.13 (m, 4H), 4.93 (q, J = 7.2 Hz, 1H), 4.30 (q, J = 6.8 Hz, 1H), 1.50-1.47 (m, 6H), 1.41-1.36 (m, 6H), 1.07 (s, 9H); ^{13}C NMR (400MHz, $CDCl_3$) δ 173.12, 169.94, 169.65, 135.74, 135.08, 133.07, 129.77, 128.60, 128.49, 128.23, 127.64, 69.20, 68.79, 68.48, 68.23, 67.17, 26.78, 21.13, 19.20, 16.74, 16.56; HRMS (M+H_2O) calc mass 652.2704, found 652.2695.

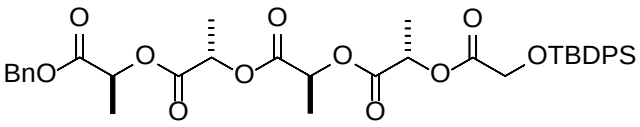


Bn-L$_R$L$_R$L$_R$G-SiR$_3$. To a stirring solution of Bn-L$_R$L$_R$L$_R$ (1.52 g, 4.70 mmol) and G-SiR_3 (2.24 g, 7.12 mmol), in CH_2Cl_2 (70 mL) was added DPTS (0.41 g, 1.40 mmol). Once the mixture became homogeneous, DCC (1.60 g, 7.76 mmol) was added and the reaction was allowed to stir

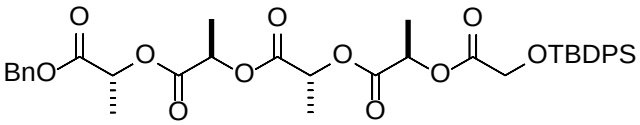
overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5% EtOAc in hexanes) to provide the product as a colorless liquid (2.71 g, 93.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.43-7.29 (m, 11H), 5.20-5.09 (m, 5H), 4.34 (d, J = 16.8 Hz, 1H), 4.28 (d, J = 16.8 Hz, 1H), 1.51 (d, J = 7.2 Hz, 6H), 1.49 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.60, 169.92, 169.89, 169.65, 135.56, 135.35, 135.07, 134.78, 132.71, 132.68, 129.87, 129.62, 128.60, 128.49, 128.23, 127.79, 69.21, 68.89, 68.42, 67.17, 61.93, 26.60, 19.24, 16.74, 16.72, 16.55; HRMS ($M+Na^+$) calc mass 643.2339, found 643.2383.



Bn-L$_R$L$_R$L$_R$L$_R$-SiR$_3$. To a stirring solution of Bn-L$_R$L$_R$ (7.99 g, 31.7 mmol) and L$_R$L$_R$-SiR$_3$ (12.98 g, 32.4 mmol), in CH_2Cl_2 (310 mL) was added DPTS (1.87 g, 6.34 mmol). Once the mixture became homogeneous, DCC (7.18 g, 34.8 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5-7.5% EtOAc in hexanes) to provide the product as a colorless liquid (18.61 g, 92.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.44-7.28 (m, 11H), 5.17 (d, J = 12.0 Hz, 1H), 5.13 (q, J = 7.2 Hz, 2H) 5.10 (d, J = 12.4 Hz, 1H), 4.92 (q, J = 7.1 Hz, 1H), 4.31 (q, J = 6.7 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H), 1.48 (d, J = 7.2 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.13, 169.94 (2), 169.66, 135.94, 135.73, 135.05, 133.40, 133.04, 129.77, 128.60, 128.49, 128.23, 127.63, 127.55, 69.19, 68.78, 68.45, 68.21, 67.17, 26.76, 21.13, 19.19, 16.73, 16.55 (2); HRMS ($M+Na^+$) calc mass 657.2496, found 657.2525.

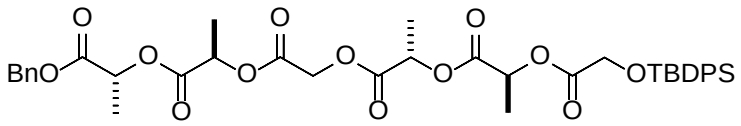


Bn-LLLLG-SiR$_3$. Prepared by Michael A. Washington. To a stirring solution of Bn-L (2.92 g, 16.2 mmol) and LLLG-SiR$_3$ (7.79 g, 14.7 mmol), in CH_2Cl_2 (150 mL) was added DPTS (0.86 g, 2.94 mmol). Once the mixture became homogeneous, DCC (3.35 g, 16.2 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 2.5-5% EtOAc in hexanes) to provide the product as a colorless liquid (8.62 g, 84.8%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.41-7.31 (m, 11H), 5.20-5.09 (m, 6H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.57-1.49 (m, 12H), 1.06 (s, 9H). ^{13}C NMR (400MHz, $CDCl_3$) δ 170.61, 169.90, 169.70, 169.55, 135.54, 135.07, 132.70, 129.88, 128.61, 128.51, 128.24, 127.80, 69.25, 68.96, 68.88, 68.42, 67.20, 61.95, 26.61, 19.25, 16.74, 16.63, 16.57; HRMS (M+H_2O) calc mass 710.2767, found 710.2759.

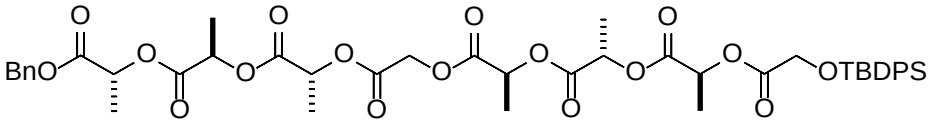


Bn-L$_R$L$_R$L$_R$L$_R$G-SiR$_3$. To a stirring solution of Bn-L$_R$L$_R$L$_R$L$_R$ (10.44 g, 26.3 mmol) and G-SiR$_3$ (9.19 g, 29.2 mmol), in CH_2Cl_2 (260 mL) was added DPTS (1.55 g, 5.27 mmol). Once the mixture became homogeneous, DCC (5.98 g, 29.0 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5-7.5% EtOAc in hexanes) to provide the product as a colorless liquid (10.49 g, 57.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.43-7.29 (m, 11H), 5.19-5.09 (m, 3H), 5.17 (q, J = 7.1 Hz, 1H), 5.16 (q, J = 7.1 Hz, 1H), 5.12 (q, J = 7.1 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.4 Hz, 1H), 1.56 (d, J =

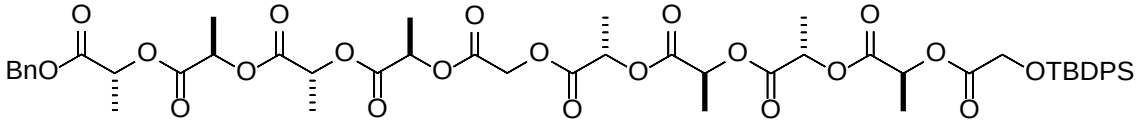
7.2 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.11, 169.90 (2), 169.70, 169.55, 135.57, 135.53, 135.07, 132.73, 132.69, 129.88, 128.60, 128.51, 128.24, 127.79, 127.77, 69.25, 68.95, 68.88, 68.42, 67.19, 61.95, 26.61, 19.25, 16.73, 16.62, 16.56; HRMS ($M+NH_4^+$) calc mass 710.2997, found 710.2963.



Bn-L*R*L*R*GLLG-SiR3. To a stirring solution of Bn-L*R*L*R*G (2.16 g, 6.97 mmol) and LLG-SiR_3 (2.88 g, 6.28 mmol), in CH_2Cl_2 (65 mL) was added DPTS (0.37 g, 1.27 mmol). Once the mixture became homogeneous, DCC (1.45 g, 7.02 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to provide the product as a colorless liquid (3.51 g, 74.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.43-7.29 (m, 11H), 5.22 (q, J = 7.1 Hz, 1H), 5.18 (q, J = 7.1 Hz, 1H), 5.17 (q, J = 7.1 Hz, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.12 (q, J = 6.9 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.56 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 7.2 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.60, 169.88, 169.77, 169.52, 169.33, 166.44, 135.56, 135.53, 135.05, 132.71, 132.66, 129.88, 128.61, 128.51, 128.22, 127.80, 127.77, 69.30, 69.19, 68.83, 68.40, 67.20, 61.93, 60.73, 26.60, 19.24, 16.72, 16.68, 16.61; HRMS ($M+Na^+$) calc mass 773.2605, found 773.2574.



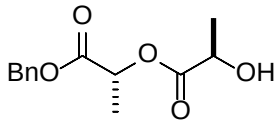
Bn-L*R*L*R*L*R*GLLLG-SiR3. To a stirring solution of Bn-L*R*L*R*L*R*G (0.199 g, 0.52 mmol) and LLLG-SiR_3 (0.25 g, 0.47 mmol), in CH_2Cl_2 (4.7 mL) was added DPTS (0.03 g, 0.10 mmol). Once the mixture became homogeneous, DCC (0.12 g, 0.58 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 15% EtOAc in hexanes) to provide the product as a colorless liquid (0.33 g, 77.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.43-7.29 (m, 11H), 5.23-5.09 (m, 8H), 4.79 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H), 1.557 (d, J = 6.8 Hz, 6H), 1.51 (d, J = 7.2 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.07 s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.60, 169.88, 169.60, 169.51, 169.43, 169.36, 166.44, 135.57, 135.54, 135.07, 132.74, 132.71, 129.88, 128.61, 128.51, 128.23, 127.80, 127.78, 69.27, 69.19, 68.91, 68.87, 68.42, 67.20, 61.95, 60.75, 26.62, 19.25, 16.73, 16.67, 16.58, 16.53, 14.19; HRMS ($M+Na^+$) calc mass 917.3028, found 917.3062.



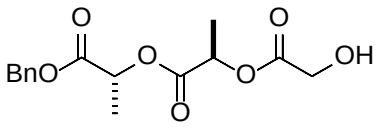
Bn-L*R*L*R*L*R*L*R*GLLLLG-SiR3. To a stirring solution of Bn-L*R*L*R*L*R*L*R*G (0.52 g, 1.1 mmol) and LLLLG-SiR_3 (0.61 g, 1.0 mmol), in CH_2Cl_2 (10 mL) was added DPTS (0.06 g, 0.21 mmol). Once the mixture became homogeneous, DCC (0.23 g, 1.1 mmol) was added and the reaction was allowed to stir overnight. The solution was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 20% EtOAc in hexanes) to provide the product as a colorless liquid (0.93 g, 88.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-

7.65 (m, 4H), 7.43-7.29 (m, 11H), 5.21-5.09 (m, 10H), 4.79 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.57 (m, 15H), 1.50 (d, J = 6.8 Hz, 1H), 1.499 (d, J = 6.8 Hz, 1H), 1.49 (d, J = 6.8 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.59, 169.90, 169.87, 169.70, 169.55, 169.50 (2), 169.39, 169.36, 166.43, 135.56, 135.52, 132.72, 132.68, 129.87, 128.60, 128.51, 128.23, 127.79, 127.77, 69.26, 69.18, 69.08, 69.00, 68.93 (2), 68.87, 68.41, 67.19, 61.93, 60.74, 26.60, 19.24, 16.72 (2), 16.67, 16.59 (4), 16.55, 14.18; HRMS ($M+Na^+$) calc mass 1061.34451, found 1061.34635.

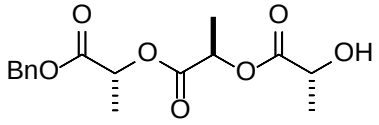
5.5.3.2 Silyl deprotection of di-protected segmers



Bn-L$_R$L$_R$. To a stirring solution of Bn-L$_R$L$_R$-SiR$_3$ (25.0 g, 50.9 mmol) in THF (500 mL) under N_2 was slowly added acetic acid (5.25 mL, 91.7 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 76.4 mL, 76.4 mmol). The reaction was stirred for 55 min and then brine (450 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 300 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (300 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 7.5% EtOAc in hexanes as the eluent to provide the product as a white solid (12.4 g, 96.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 5.21 (q, J = 7.1 Hz, 1H), 5.18 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.0 Hz, 1H), 4.35-4.29 (m, 1H), 2.72 (d, J = 5.2 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.42 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.10, 169.96, 135.04, 128.61, 128.52, 128.22, 69.37, 67.23, 66.67, 20.41, 16.80; HRMS ($M+Na^+$) calc mass 275.0895, found 275.0894.

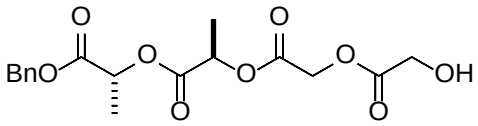


Bn-L*R*L*R*G. To a stirring solution of Bn-L*R*L*R*G-SiR$_3$ (8.13 g, 14.8 mmol) in THF (200 mL) under N_2 was slowly added acetic acid (6.8 mL, 119 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 22.2 mL, 22.2 mmol). The reaction was stirred for 90 min and then brine (200 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 150 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (200 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 10-25% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (4.24 g, 92.1%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.21 (q, J = 7.0 Hz, 1H), 5.20 (q, J = 7.0 Hz, 1H), 5.17 (d, J = 12.0 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 4.26 (d, J = 17.0 Hz, 1H), 4.20 (d, J = 17.5 Hz, 1H), 2.37 (br s, 1H), 1.517 (d, J = 7.0 Hz, 3H), 1.516 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.68, 169.88, 169.60, 135.04, 128.61, 128.52, 128.23, 69.33, 69.16, 67.23, 60.47, 16.75, 16.67; HRMS ($M+Na^+$) calc mass 333.0950, found 333.0963.

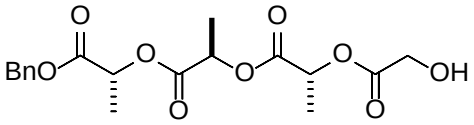


Bn-L*R*L*R*L*R*. To a stirring solution of Bn-L*R*L*R*L*R*-SiR$_3$ (13.90 g, 24.7 mmol) in THF (250 mL) under N_2 was slowly added acetic acid (2.5 mL, 43.7 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 37.0 mL, 37.0 mmol). The reaction was stirred for 85 min and then brine (250 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 200 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (250 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then

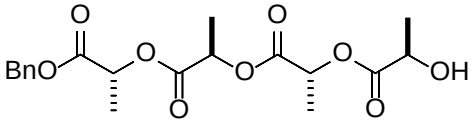
chromatographed over silica using 10-25% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (7.70 g, 96.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.19 (q, J = 7.1 Hz, 2H), 5.18 (d, J = 12.8 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 4.36-4.30 (m, 1H), 2.69-2.68 (m, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.51 (d, J = 7.2 Hz, 3H), 1.47 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.09, 169.88, 169.57, 135.05, 128.64, 128.60, 128.51, 128.25, 69.29, 69.08, 67.22, 66.69, 20.48, 16.75, 16.64; HRMS ($M+Na^+$) calc mass 347.1107, found 347.1100.



Bn-L*R*L*R*GG. To a stirring solution of Bn-L*R*L*R*GG-SiR_3 (3.26 g, 5.3 mmol) in THF (54 mL) under N_2 was slowly added acetic acid (2.5 mL, 39.7 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 8.1 mL, 8.1 mmol). The reaction was stirred for 90 min and then brine (50 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 50 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (50 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 7.5-25% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (1.16 g, 58.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.19 (q, J = 7.1 Hz, 1H), 5.186 (q, J = 7.1 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 4.82 (d, J = 16.0 Hz, 1H), 4.75 (d, J = 16.0 Hz, 1H), 4.33-4.22 (m, 2H), 2.38 (t, J = 5.8 Hz, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.509 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.59, 169.86, 169.36, 166.65, 135.03, 128.61, 128.52, 128.22, 69.34, 69.32, 67.23, 60.83, 16.73, 16.61; HRMS ($M+H^+$) calc mass 369.1173, found 369.1186.

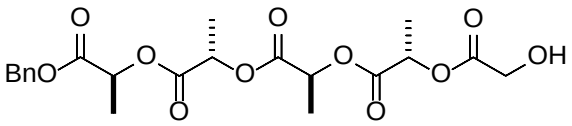


Bn-L*R*L*R*L*R*G. To a stirring solution of Bn-L*R*L*R*L*R*G-SiR$_3$ (2.69 g, 4.34 mmol) in THF (45 mL) under N_2 was slowly added acetic acid (2.0 mL, 35 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 6.5 mL, 6.5 mmol). The reaction was stirred for 90 min and then brine (50 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 50 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (50 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 12.5-35% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (1.59 g, 96.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.22 (q, J = 7.2 Hz, 1H) 5.17 (q, J = 7.2 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.16 (q, J = 6.9 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.20 (d, J = 17.2 Hz, 1H), 2.41 (br s, 1H), 1.57 (d, J = 7.2 Hz, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.67, 169.87, 169.64, 169.50, 135.03, 128.59, 128.50, 128.22, 69.27, 69.11, 69.09, 67.20, 60.36, 16.72 (2), 16.56; HRMS ($M+Na^+$) calc mass 405.1162, found 405.1145.

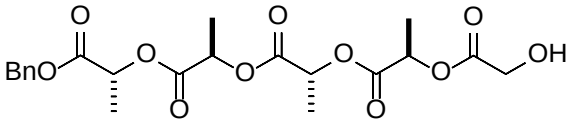


Bn-L*R*L*R*L*R*L*R*. To a stirring solution of Bn-L*R*L*R*L*R*L*R*-SiR$_3$ (17.21 g, 27.1 mmol) in THF (275 mL) under N_2 was slowly added acetic acid (2.8 mL, 49 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 40.7 mL, 40.7 mmol). The reaction was stirred for 70 min and then brine (275 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 250 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (250 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then

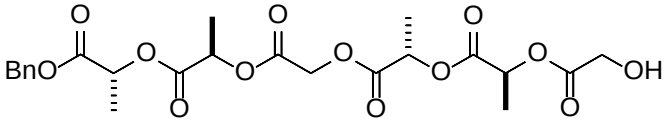
chromatographed over silica using 10-25% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (10.48 g, 97.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 5.23-5.14 (m, 4H), 5.11 (d, J = 12.5 Hz, 1H), 4.36-4.31 (m, 1H), 2.68 (m, 1H), 1.57 (d, J = 7.0 Hz, 3H), 1.51 (d, J = 7.0 Hz, 3H), 1.50 (d, J = 7.0 Hz, 3H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.10, 169.88, 169.61, 169.50, 135.08, 128.60, 128.51, 128.23, 69.28, 69.08, 69.04, 67.20, 66.70, 20.49, 16.73, 16.70, 16.57; HRMS ($M+H^+$) calc mass 397.1499, found 397.1498.



Bn-LLLLG. Prepared by Michael A. Washington. To a stirring solution of Bn-LLLLG-SiR_3 (6.89 g, 9.95 mmol) in THF (100 mL) under N_2 was slowly added acetic acid (5.0 mL, 79.6 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 14.9 mL, 14.9 mmol). The reaction was stirred for 60 min and then brine (250 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 225 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (250 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 10-15% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (3.65 g, 80.8%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 5.17 (m, 6H), 4.27 (d, 1H), 4.21 (d, 1H), 2.41 (s, 1H), 1.58 (m, 6H), 1.50 (m, 6H). ^{13}C NMR (400MHz, CDCl3) δ 172.65, 169.86, 169.64, 169.52, 135.02, 128.58, 128.48, 128.21, 69.26. 69.09, 67.18, 60.45, 25.94, 16.71, 16.62, 16.53, 14.16; HRMS ($M+NH_4^+$) calc mass 472.1775, found 472.1819.



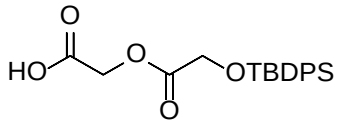
Bn-L*R*L*R*L*R*L*R*G. To a stirring solution of Bn-L*R*L*R*L*R*L*R*G-SiR$_3$ (10.83 g, 15.6 mmol) in THF (155 mL) under N_2 was slowly added acetic acid (7.1 mL, 124 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 23.5 mL, 23.5 mmol). The reaction was stirred for 90 min and then brine (250 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 225 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (250 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then chromatographed over silica using 10-30% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (6.43 g, 90.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 5.22 (q, J = 7.1 Hz, 1H), 5.20-5.12 (m, 4H), 5.11 (d, J = 12.0 Hz, 1H), 4.29-4.18 (m, 2H), 2.37-2.34 (m, 1H), 1.58 (d, J = 7.2 Hz, 6H), 1.51-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.69, 169.88, 169.64, 169.54, 169.50, 135.05, 128.60, 128.51, 128.22, 69.27, 69.14, 69.09, 69.02, 67.20, 60.47, 16.73 (2), 16.64, 16.55; HRMS ($M+NH_4^+$) calc mass 472.1819, found 472.1794.



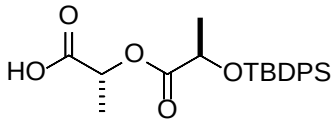
Bn-L*R*L*R*GLLG. To a stirring solution of Bn-L*R*L*R*GLLG-SiR$_3$ (3.13 g, 4.17 mmol) in THF (40 mL) under N_2 was slowly added acetic acid (1.9 mL, 33 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 6.2 mL, 6.2 mmol). The reaction was stirred for 60 min and then brine (50 mL) was added. The resulting aqueous layer was extracted with diethyl ether (3 x 40 mL), the combined organic layers were washed with aqueous saturated sodium bicarbonate solution (125 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The concentrate was then

chromatographed over silica using 20-35% EtOAc in hexanes as the eluent to provide the product as a colorless liquid (1.96 g, 91.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.24 (q, J = 7.1 Hz, 1H), 5.21 (q, J = 7.2 Hz, 1H), 5.18 (q, J = 7.2 Hz, 1H), 5.17 (q, J = 7.1 Hz, 1H), 5.16 (d, J = 12.4 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.28-4.17 (m, 2H), 2.47 (s, 1H), 1.564 (d, J = 7.2 Hz, 3H), 1.562 (d, J = 7.2 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62, 169.86, 169.52, 169.36, 169.33, 166.43, 135.02, 128.58, 128.48, 128.20, 69.31, 69.20, 69.07, 68.97, 67.18, 60.75, 60.43, 16.68 (3), 16.56; HRMS ($M+NH_4^+$) calc mass 535.1428, found 535.1450.

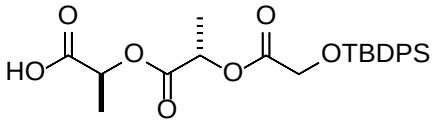
5.5.3.3 Hydrogenolysis of di-protected segmers



GG-SiR$_3$. To a stirring solution of Bn-GG-SiR_3 (10.66 g, 23.0 mmol) in EtOAc (230 mL) under N_2 was added 10% Pd/C (0.53 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to provide the product as a colorless solid (6.46 g, 75.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H), 7.69-7.67 (m, 4H), 7.45-7.35 (m, 6H), 4.66 (s, 2H), 4.36 (s, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.32, 170.62, 135.54, 132.56, 129.96, 127.82, 61.82, 60.08, 26.61, 19.24; HRMS ($M+NH_4^+$) calc mass 390.17313, found 390.17159.

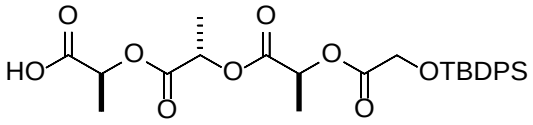


L_RL_R-SiR$_3$. To a stirring solution of Bn-L_RL_R-SiR$_3$ (18.2g, 37.1 mmol) in EtOAc (370 mL) under N_2 was added 10% Pd/C (0.91 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to provide the product as a colorless liquid (13.0 g, 87.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (br s, 1H), 7.68-7.65 (m, 4H), 7.44-7.32 (m, 6H), 4.93 (q, J = 7.2 Hz, 1H), 4.32 (q, J = 6.7 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.36 (d, J = 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.29, 173.11, 135.95, 135.74, 133.40, 132.98, 129.79, 127.64, 127.56, 68.51, 68.09, 26.76, 21.08, 19.19, 16.58; HRMS ($M\text{-}H^+$) calc mass 399.1628, found 399.1629.

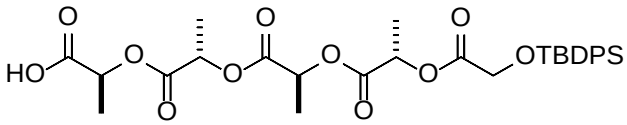


LLG-SiR$_3$. To a stirring solution of Bn-LLG-SiR$_3$ (7.63 g, 13.9 mmol) in EtOAc (140 mL) under N_2 was added 10% Pd/C (0.76 g, 5% w/w). The reaction vessel was purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. The reaction mixture was placed under N_2, the mixture was filtered over celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 7.5% EtOAc in hexanes) to provide the product as a colorless liquid (2.92 g, 45.7%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 7.68-7.65 (m, 4H), 7.43-7.35 (m, 6H), 5.19 (q, J = 7.2 Hz, 1H), 5.13 (q, J = 7.0 Hz, 1H), 4.35 (d, J = 17 Hz, 1H), 4.29 (d, J = 16.5 Hz, 1H), 1.53 (d, J = 7.0 Hz, 3H), 1.48 (d, J = 7.5 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.43, 170.70, 169.80, 135.56, 135.53, 132.71, 132.66, 129.90, 127.80, 127.78, 68.62, 68.43, 61.95, 60.47, 26.61, ; HRMS ($M\text{-}H^+$) calc mass 457.1683, found 457.1642.



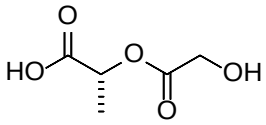
LLLG-SiR$_3$. To a stirring solution of Bn-LLLG-SiR_3 (1.47 g, 2.4 mmol) in EtOAc (25 mL) under N_2 was added 10% Pd/C (0.073 g, 5% w/w). The reaction vessel was purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. The reaction mixture was placed under N_2, the mixture was filtered over celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% EtOAc in hexanes) to provide the product as a colorless liquid (1.02 g, 81.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.68-7.64 (m, 4H), 7.43-7.34 (m, 6H), 5.20 (m, 3H), 4.34 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 1.55 (d, J = 7.2 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.31, 170.67, 169.95, 169.64, 135.56, 135.53, 132.69, 132.66, 129.89, 127.80, 127.78, 68.87, 68.45, 61.93, 60.45, 26.60, 19.24, 16.71, 16.64, 16.56, 14.17; HRMS ($M\text{-}H^+$) calc mass 529.1894, found 529.1870.



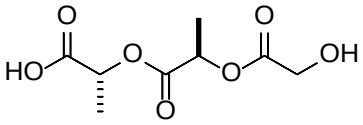
LLLLG-SiR$_3$. To a stirring solution of Bn-LLLLG-SiR_3 (1.58 g, 2.2 mmol) in EtOAc (21 mL) under N_2 was added 10% Pd/C (0.087 g, 5% w/w). The reaction vessel was purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. The reaction mixture was placed under N_2, the mixture was filtered over celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 10% EtOAc in hexanes) to provide the product as a

colorless liquid (0.64 g, 48.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 7.68-7.65 (m, 4H), 7.43-7.34 (m, 6H), 5.20-5.10 (m, 4H), 4.34 (d, J = 16.8 Hz, 1H), 4.28 (d, J = 16.8 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H), 1.56 (d, J = 7.2 Hz, 3H), 1.53 (d, J = 7.2 Hz, 3H), 1.50 (d, J = 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.42, 170.65, 169.93, 169.75, 169.55, 135.56, 135.53, 132.70, 132.67, 129.88, 127.80, 127.78, 68.92, 68.89, 68.72, 68.43, 61.94, 26.60, 19.24, 16.72, 16.61 (2), 16.56; HRMS ($M\text{-}H^+$) calc mass 601.20996, found 601.21241.

5.5.3.4 Hydrogenolysis of mono-protected segmers

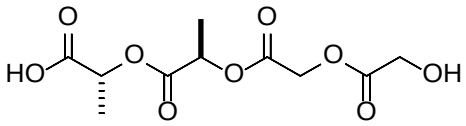


L*R*G. To a stirring solution of Bn-L*R*G (1.36 g, 5.7 mmol) in EtOAc (60 mL) under N_2 was added 10% Pd/C (0.07g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless liquid (0.83 g, 98.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (br s, 2H), 5.21 (q, J = 7.1 Hz, 1H), 4.29 (d, J = 17.2 Hz, 1H), 4.23 (d, J = 17. Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.00, 172.78, 68.98, 60.37, 16.67; HRMS ($M\text{-}H^+$) calc mass 147.02855, found 147.02880.

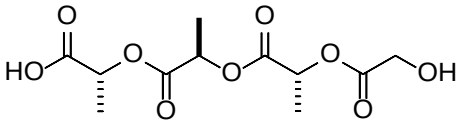


L*R*L*R*G. To a stirring solution of Bn-L*R*L*R*G (2.00 g, 6.46 mmol) in EtOAc (65 mL) under N_2 was added 10% Pd/C (0.15 g, 7% w/w). The reaction vessel was then purged twice with a H_2

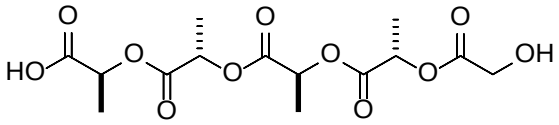
balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless liquid (1.31 g, 92.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (br s, 2H), 5.22 (q, J = 6.9 Hz, 1H), 5.17 (q, J = 7.0 Hz, 1H), 4.29 (d, J = 17.6 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.98, 172.82, 169.70, 69.20, 68.94, 60.43, 16.66, 16.64; HRMS ($M+Na^+$) calc mass 243.0481, found 243.0491.



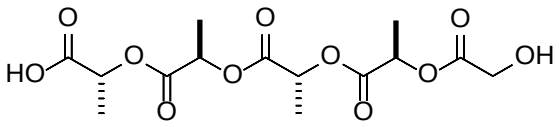
L_RL_RGG. To a stirring solution of Bn-L_RL_RGG (0.95 g, 2.6 mmol) in EtOAc (26 mL) under N_2 was added 10% Pd/C (0.57 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless liquid (0.70 g, 97.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (br s, 2H), 5.20 (q, J = 7.2 Hz, 1H), 5.16 (q, J = 7.1 Hz, 1H), 4.84 (d, J = 16.0 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.28 (s, 2H), 1.56 (d, J = 7.2 Hz, 3H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.94, 172.64, 169.40, 166.83, 69.35, 68.92, 60.82, 60.35, 16.60 (2); HRMS ($M+H^+$) calc mass 369.1186, found 369.1173.



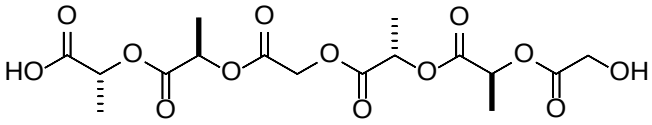
$L_RL_RL_RG$. To a stirring solution of Bn-$L_RL_RL_RG$ (2.10 g, 5.49 mmol) in EtOAc (55 mL) under N_2 was added 10% Pd/C (0.36 g, 17% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 35-60% EtOAc in hexanes) to provide the product as a colorless liquid (1.34 g, 83.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (q, J = 7.0 Hz, 1H), 5.18 (q, J = 7.0 Hz, 1H), 5.15 (q, J = 7.2 Hz, 1H), 4.28 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H), 1.57 (d, J = 7.2 Hz, 3H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.15, 172.76, 169.76, 169.53, 69.16, 69.11, 68.81, 60.42, 16.71, 16.61, 16.57; HRMS ($M\text{-}H^+$) calc mass 291.0716, found 291.0741.



LLLLG. Prepared by Michael A. Washington. To a stirring solution of Bn-LLLLG (3.65 g, 8.04 mmol) in EtOAc (80 mL) under N_2 was added 10% Pd/C (0.0.20 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless solid (2.71 g, 92.5%). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.20 (m, 4H), 4.24 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 1.56 (m, 9H). ^{13}C NMR (400MHz, $CDCl_3$) δ 174.57, 172.76, 169.68, 169.57, 169.54, 69.20, 69.14, 69.07, 68.89, 60.46, 16.74, 16.65, 16.59; HRMS ($M+H^+$) calc mass 365.1097, found 365.1084.

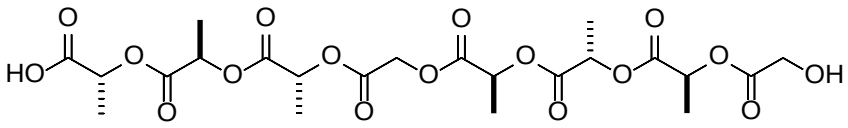


$L_RL_RL_RL_RG$. To a stirring solution of Bn-$L_RL_RL_RL_RG$ (5.20 g, 11.5 mmol) in EtOAc (115 mL) under N_2 was added 10% Pd/C (0.27 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless solid (4.07 g, 97.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (br s, 2H), 5.22 (q, J = 7.1 Hz, 1H), 5.18 (q, J = 7.2 Hz, 1H), 5.16 (q, J = 7.2 Hz, 1H), 5.14 (q, J = 7.2 Hz, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.6 Hz, 1H), 1.58 (d, J = 7.2 Hz, 3H), 1.57 (d, J = 7.2 Hz, 3H), 1.56 (d, J = 7.2 Hz, 3H), 1.53 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.07, 172.74, 169.70, 169.57, 169.52, 69.17, 69.13, 69.02, 68.79, 60.44, 16.73, 16.62 (2), 16.57; HRMS (M-H^+) calc mass 363.09390, found 363.09219.

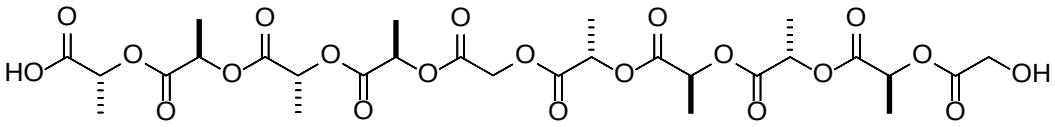


L_RL_RGLLG. To a stirring solution of Bn-L_RL_RGLLG (1.90 g, 3.71 mmol) in EtOAc (40 mL) under N_2 was added 10% Pd/C (0.10 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless liquid (1.47 g, 94.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (br s, 2H), 5.23 (q, J = 7.1 Hz, 1H), 5.21 (q, J = 7.1 Hz, 1H), 5.18 (q, J = 7.1 Hz, 1H), 5.15 (q, J = 7.2 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 17.6 Hz, 1H), 4.21 (J = 17.6 Hz, 1H), 1.564

(d, J = 7.2 Hz, 3H), 1.560 (d, J = 7.2 Hz, 3H), 1.55 (d, J = 7.2 Hz, 3H), 1.53 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.56, 172.69, 169.57, 169.41, 169.31, 166.54, 69.25, 69.15, 69.03, 68.90, 60.78, 60.40, 16.69, 16.65, 16.61, 16.57; HRMS ($M+Na^+$) calc mass 445.0935, found 445.0958.



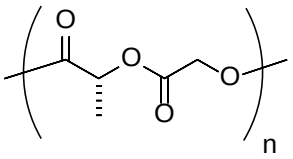
L*R*L*R*L*R*GLLLG. To a stirring solution of Bn-L*R*L*R*L*R*GLLLG (1.19 g, 1.8 mmol) in EtOAc (18 mL) under N_2 was added 10% Pd/C (0.06 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as a colorless solid (0.99 g, 97.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (br s, 2H), 5.24-5.11 (m, 6H), 4.79 (d, J = 16.0 Hz, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 1.58-1.52 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.95, 172.75, 169.68, 169.51, 169.48, 169.43, 169.40, 166.48, 69.19, 69.16, 69.12, 69.08, 68.98, 68.78, 60.76, 60.43, 16.71 (2), 16.64, 16.62, 16.59, 16.53; HRMS ($M+Na^+$) calc mass 589.1395, found 589.1381.



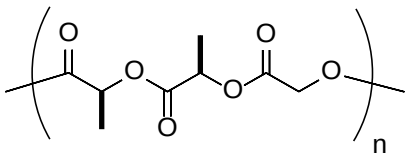
L*R*L*R*L*R*L*R*GLLLLG. To a stirring solution of Bn-L*R*L*R*L*R*L*R*GLLLLG (0.52 g, 0.65 mmol) in EtOAc (7 mL) under N_2 was added 10% Pd/C (0.03 g, 5% w/w). The reaction vessel was then purged twice with a H_2 balloon and allowed to stir overnight under 1 atm H_2. Once the reaction had completed, the vessel was evacuated and filled with N_2 and the mixture was filtered over celite, dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to provide the product as

a colorless solid (0.46, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (br s, 2H), 5.24-5.11 (m, 8H), 4.79 (d, J = 16.0, 1H), 4.66 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 17.6 Hz, 1H), 4.21 (d, J = 17.6 Hz, 1H), 1.58-1.52 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.48, 172.74, 169.68, 169.58, 169.56, 169.50, 169.46, 169.40 (2), 166.45, 69.81, 69.16, 69.11, 69.02, 69.00, 68.98, 68.83, 60.77, 16.72, 16.69, 16.63 (3), 16.57 (3); HRMS ($M\text{-}H^+$) calc mass 709.18218, found 709.18350.

5.5.3.5 SAP of sequenced segmers

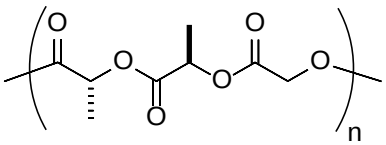


Poly L*R*G. Under N_2, L*R*G (0.81 g, 5.4 mmol) and DPTS (0.32 g, 1.1 mmol) were dissolved in CH2Cl2 (1.82 mL) and cooled to 0 ºC. DIC (1.28 mL, 8.2 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.33 g, 46.0%). ^{1}H NMR (400 MHz, CDCl3) δ 5.22 (q, J = 6.8 Hz, 1H), 4.85 (d, J = 16.0 Hz, 1H), 4.62 (d, J = 16.0 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 169.35, 166.42, 69.13, 60.80, 16.71; SEC (THF): M_n – 23.0 kDa, M_w – 32.0 kDa, Đ - 1.39.

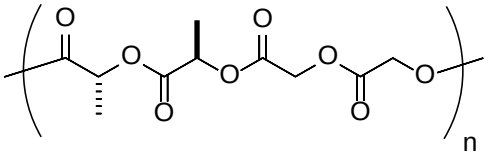


Poly LL*R*G. Under N_2, LL_RG (1.35 g, 6.1 mmol) and DPTS (0.36 g, 1.2 mmol) were dissolved in CH_2Cl_2 (2.0 mL) and cooled to 0 ºC. DIC (1.44 mL, 14.2 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.93 g, 75.4%). ^{1}H NMR (600

MHz, $CDCl_3$) δ 5.20 (q, J = 7.2; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.35, 166.42, 69.13, 60.80, 16.71; SEC (THF): M_n – 30.3 kDa, M_w – 40.3 kDa, Đ - 1.33.

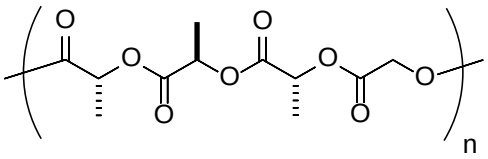


Poly L_RL_RG. Under N_2, L_RL_RG (1.27 g, 5.7 mmol) and DPTS (0.35 g, 1.19 mmol) were dissolved in CH2Cl2 (1.92 mL) and cooled to 0 ºC. DIC (1.36 mL, 13.4 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.95 g, 81.1%). 1H NMR (600 MHz, CDCl3) δ 5.20 (q, J = 7.2 Hz, 1H), 5.17 (d, J = 7.2 Hz, 1H), 4.85 (d, J = 15.6 Hz, 1H), 4.60 (d, J = 16.2 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H), 1.56 (d, J = 7.2 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 169.49, 169.37, 166.49, 69.17, 68.98, 60.75, 16.67, 16.63; SEC (THF): M_n – 26.2 kDa, M_w – 38.4 kDa, Đ - 1.47.

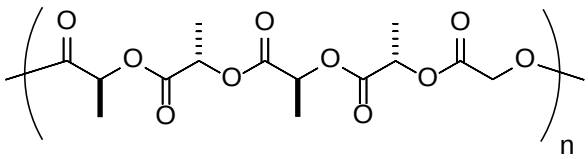


Poly L_RL_RGG. Under N_2, L_RL_RGG (0.67 g, 2.4 mmol) and DPTS (0.14 g, 0.48 mmol) were dissolved in CH_2Cl_2 (0.8 mL) and cooled to 0 ºC. DIC (0.56 mL, 5.5 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.47 g, 76.0%). ^1H NMR (600 MHz, $CDCl_3$) δ 5.22 (q, J = 7.2 Hz, 1H), 5.18 (q, J = 7.2 Hz, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.80 (d, J = 16.2 Hz, 1H), 4.70 (d, J = 16.2 Hz, 1H), 4.66 (d, J = 16.2 Hz, 1H), 1.57 (d, J = 6.0 Hz,

3H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.41, 169.31, 166.44, 166.41, 69.28, 69.00, 60.85, 60.66, 16.67, 16.61; SEC (THF): M_n – 25.1 kDa, M_w – 35.3 kDa, Đ - 1.40.

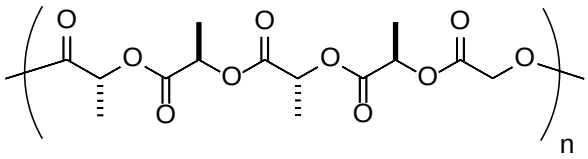


Poly $L_RL_RL_RG$. Under N_2, $L_RL_RL_RG$ (1.30 g, 4.5 mmol) and DPTS (0.27 g, 0.92 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 ºC. DIC (1.05 mL, 10.3 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.99 g, 80.6%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.19 (q, J = 7.0 Hz, 1H), 5.17 (q, J = 7.0 Hz, 1H), 5.15 (q, J = 7.0 Hz, 1H), 4.85 (d, J = 16.1 Hz, 1H), 4.59 (d, J = 16.1 Hz, 1H), 1.564 (d, J = 7.0 Hz, 3H), 1.561 (d, J = 7.0 Hz, 3H), 1.52 (d, J = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.50 (2), 169.45, 166.49, 69.18, 69.08, 68.93, 60.77, 16.69 16.65, 16.58; SEC (THF): M_n – 31.9 kDa, M_w – 43.2 kDa, Đ - 1.4.

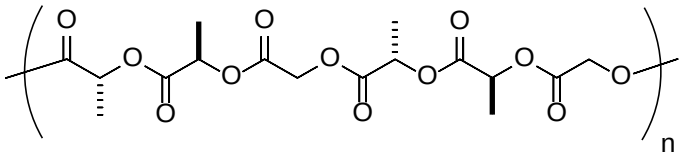


Poly LLLLG. Prepared by Michael A. Washington. Under N_2, LLLLG (2.71 g, 7.44 mmol) and DPTS (0.44 g, 1.51 mmol) were dissolved in 1:1 CH_2Cl_2/DMF (1.24 mL and 1.24 mL) and cooled to 0 ºC. DIC (1.74 mL, 11.1 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (2.22 g, 81.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21-5.13 (m, 4H), 4.86 (d, J = 16.4 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 1.57-1.55 (m, 12H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 169.56, 169.51 (2), 169.45, 169.49, 69.19, 69.09, 68.99, 68.93, 60.77, 16.69, 16.66, 16.60 (2); SEC (THF): M_n – 8.8 kDa, M_w – 12.1 kDa, Đ - 1.6.

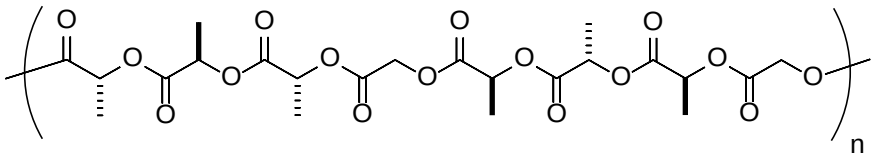


Poly $L_RL_RL_RL_RG$. Under N_2, $L_RL_RL_RL_RG$ (4.04 g, 11.0 mmol) and DPTS (0.65 g, 2.2 mmol) were dissolved in CH_2Cl_2 (1.85 mL), DMF (1.85 mL) and cooled to 0 ºC. DIC (2.6 mL, 25.6 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (3.17 g, 82.5%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.20-5.13 (m, 4H), 4.85 (d, J = 15.4 Hz, 1H), 4.59 (d, J = 16.1 Hz, 1H), 1.57-1.55 (m, 12H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.57, 169.51 (2), 169.46, 166.49, 69.17, 69.08, 68.97, 68.92, 60.75, 16.68, 16.65, 16.59 (2); SEC (THF): M_n – 6.0 kDa, M_w – 7.8 kDa, Đ -1.31.

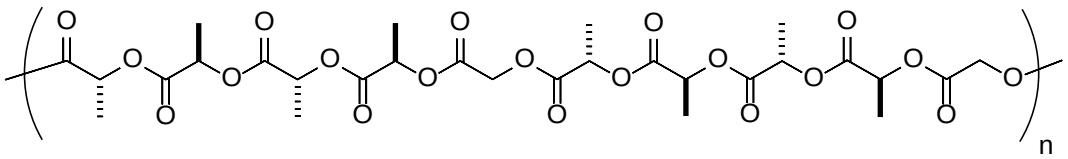


Poly L_RL_RGLLG. Under N_2, L_RL_RGLLG (1.43 g, 3.4 mmol) and DPTS (0.21 g, 0.70 mmol) were dissolved in CH_2Cl_2 (1.1 mL) and cooled to 0 ºC. DIC (0.8 mL, 7.9 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (1.16 g, 84.4%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.21 (q, J = 7.2 Hz, 1H), 5.18 (q, J = 7.2 Hz, 1H), 4.78 (d, J = 16.1 Hz, 1H), 4.67 (d, J = 16.1 Hz, 1H), 1.56 (d, J = 7.0 Hz, 3H), 1.55 (d, J = 7.0 Hz, 3H); ^{13}C NMR

(175 MHz, $CDCl_3$) δ 169.38, 169.26, 166.43, 69.17, 69.00, 60.74, 16.69, 16.63; SEC (THF): M_n – 17.1 kDa, M_w – 25.3 kDa, Đ - 1.48.



Poly $L_RL_RL_RGLLLG$. Under N_2, $L_RL_RL_RGLLLG$ (0.96 g, 1.7 mmol) and DPTS (0.10 g, 0.34 mmol) were dissolved in CH_2Cl_2 (0.57 mL) and cooled to 0 ºC. DIC (0.4 mL, 3.9 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.68 g, 73.5%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.21 (q, J = 7.0 Hz, 1H), 5.18 (q, J = 7.0 Hz, 1H), 5.16 (q, J = 7.0 Hz, 1H), 4.79 (d, J = 16.1 Hz, 1H), 4.66 (d, J = 15.4 Hz, 1H), 1.559 (d, J = 7.0 Hz, 3H), 1.558 (d, J = 7.0 Hz, 3H), 1.554 (d, J = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.45, 169.37, 166.43, 69.20, 69.10, 68.97, 60.78, 16.73, 16.67, 16.57; SEC (THF): M_n – 23.9 kDa, M_w – 30.8 kDa, Đ - 1.29.



Poly $L_RL_RL_RL_RGLLLLG$. Under N_2, $L_RL_RL_RL_RGLLLLG$ (0.43 g, 0.61 mmol) and DPTS (0.036 g, 0.12 mmol) were dissolved in CH_2Cl_2 (0.2 mL) and cooled to 0 ºC. DIC (0.14 mL, 0.14 mmol) was added dropwise by syringe and the reaction mixture was stirred for 3 h. The polymer was precipitated twice from MeOH and then dried under vacuum to yield a colorless solid (0.35 g, 82.8%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.21-5.13 (m, 4H), 4.79 (d, J = 16.1 Hz, 1H), 4.65 (d, J = 16.1 Hz, 1H), 1.55 (m, 12H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.56, 169.46, 169.38 (2),

166.42, 69.18, 69.07, 68.98, 68.95, 60.74, 16.70, 16.67, 16.58 (2); SEC (THF): M_n – 37.8 kDa, M_w – 46.9 kDa, Đ - 1.24.

5.5.4 Preparation of mixed polymer samples with opposing stereochemistry

Samples to be used in stereocomplex formation. Each individual polymer was dissolved in dry CH_2Cl_2 to give a concentration of polymer to solvent as 1g/dL. The two polymer solutions were then mixed together and vortexed. The polymer solution was then added to 500 mL of rapidly stirring MeOH. The precipitation solution was allowed to stir for 30 min. The solution appeared cloudy or a dispersed polymer powder. The solution was then filtered through a 0.45 μm nylon filter to collect the polymer powder.

APPENDIX A

A.1 SYNTHESIS OF REPEATING SEQUENCE COPOLYMERS OF LACTIC, GLYCOLIC AND CAPROLACTIC ACIDS

A.1.1 Data compiled for random PLCA, PGCA, and homopolymers PCL, PGA, and PLLA

Table 13. Numerical data compiled for the random PLCAs and the homopolymers of PLLA and PCL.[26,89,91,93-96]

Reference	Polymer	Mol % C	T_g (ºC)
Woodruff, M. A.; Hutmacher, D. W. Prog Polym Sci 2010, 35, 1217-1256.	PLLA	0	60
Choi, S. H.; Park, T. G. J Biomater Sci Polym Ed 2002, 13, 1163-1173.	PCL	100	-58
Wang, W.; Ping, P.; Chen, X.; Jing, X. J Appl Polym Sci 2007, 104, 4182-4187.	PLCA	20	19.0
		10	37.7
		5	42.0
Pappalardo, D.; Annunziata, L.; Pellecchia, C. Macromolecules 2009, 42, 6056-6062.	PLCA	6	51.0
		40	10.0
Baimark, Y.; Molloy, R. ScienceAsia 2004, 30, 327-334.	PLCA	48	-24
		48	-37
		49	-35
		49	-37
		49	-36
		49	-21
		49	-27
		48	-30
Nomura, N.; Akita, A.; Ishii, R.; Mizuno, M. J Am Chem Soc 2010, 132, 1750-1751.	PLCA	51	-15.6
Wei, Z.; Liu, L.; Qu, C.; Qi, M. Polymer 2009, 50, 1423-1429.	PLCA	8	47
		36	8
		55	-16
		77	-42

Table 14. Numerical data compiled for the random PGCAs and the homopolymers of PGA and PCL.[26,29,90-92]

Reference	Polymer	Mol % C	T_g (ºC)
Woodruff, M. A.; Hutmacher, D. W. Prog Polym Sci 2010, 35, 1217-1256.	PGA	0	35
Choi, S. H.; Park, T. G. J Biomater Sci Polym Ed 2002, 13, 1163-1173.	PCL	100	-58
Dobrzynski, P.; Kasperczyk, J.; Jelonek, K.; Ryba, M.; Walski, M.; Bero, M. J Biomed Mater Res Part A 2006, 79, 865-873.	PGCA	90	-50.1
Dobrzynski, P.; Li, S.; Kasperczyk, J.; Bero, M.; Gasc, F.; Vert, M. Biomacromolecules 2005	PGCA	17.6	-11.8
		35.1	-43.6
		36.1	-38
		56.3	-55.9
		55.0	-55.1
		55.0	-47.8
		83.5	-60
		83.5	-60
		85.2	-60.9
Bero, M.; Czapla, B.; Dobrzynski, P.; Janeczek, H.; Kasperczyk, J. Macromol Chem Phys 1999, 200, 911-916.	PGCA	4.2	12
		13.0	9.3
		19.0	1.3
		33.3	-33
		46.0	-55.5
		61.3	-57.8
		83.5	-60.3

A.1.2 H, ^{13}C NMR, and 2D NMR spectra of PGCAs, PLCAs, and PLGCAs

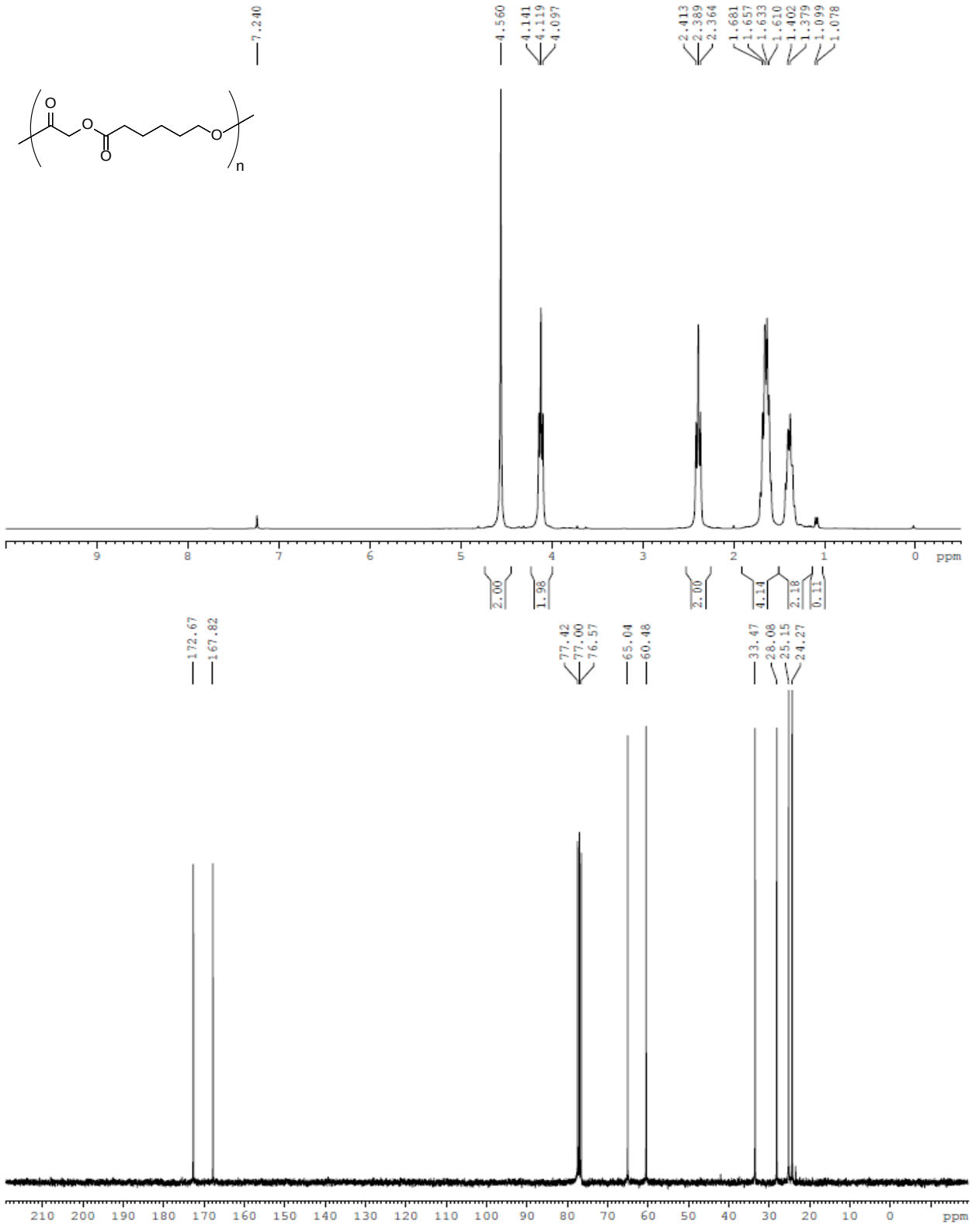


Figure 42. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly GC**.

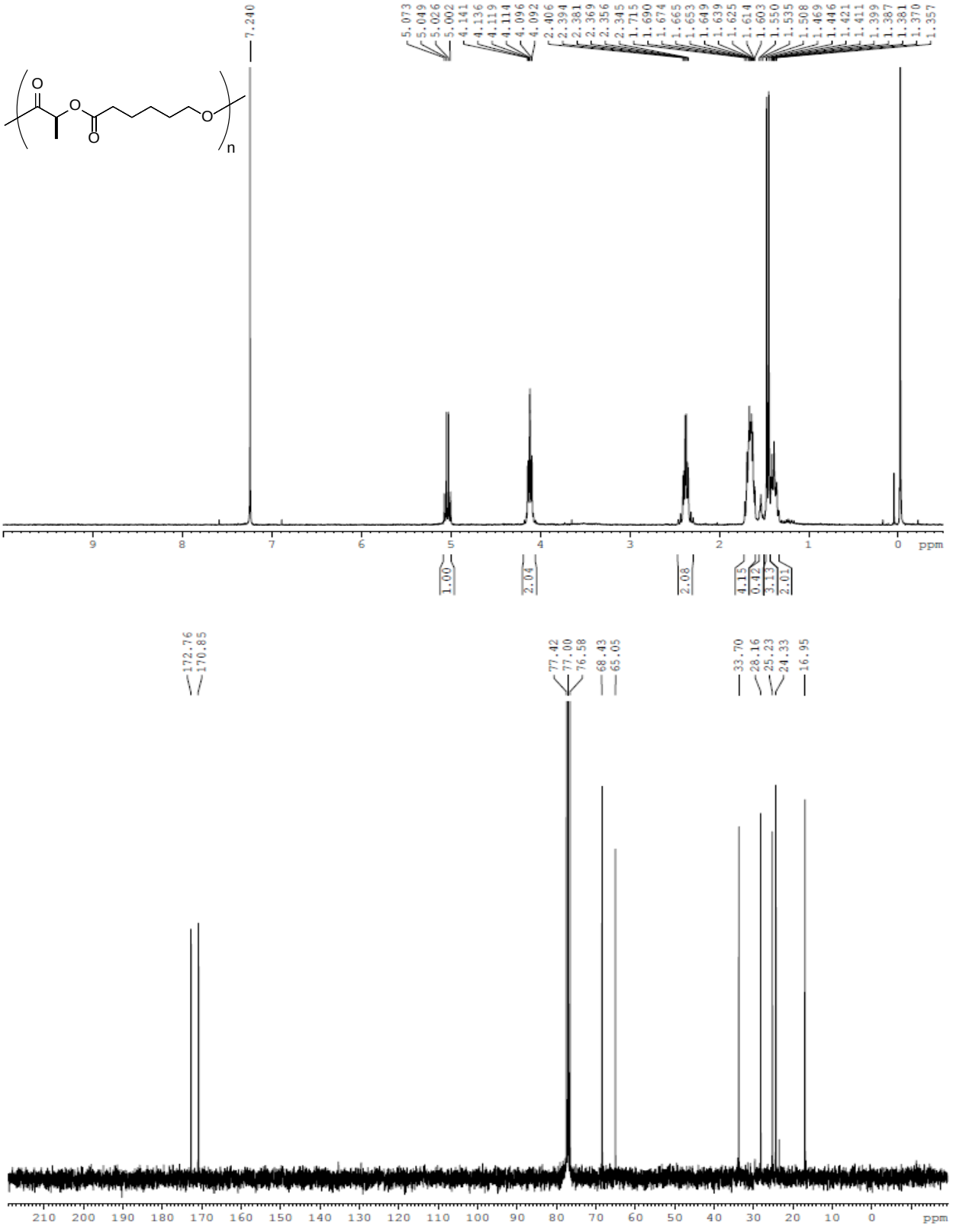


Figure 43. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LC**.

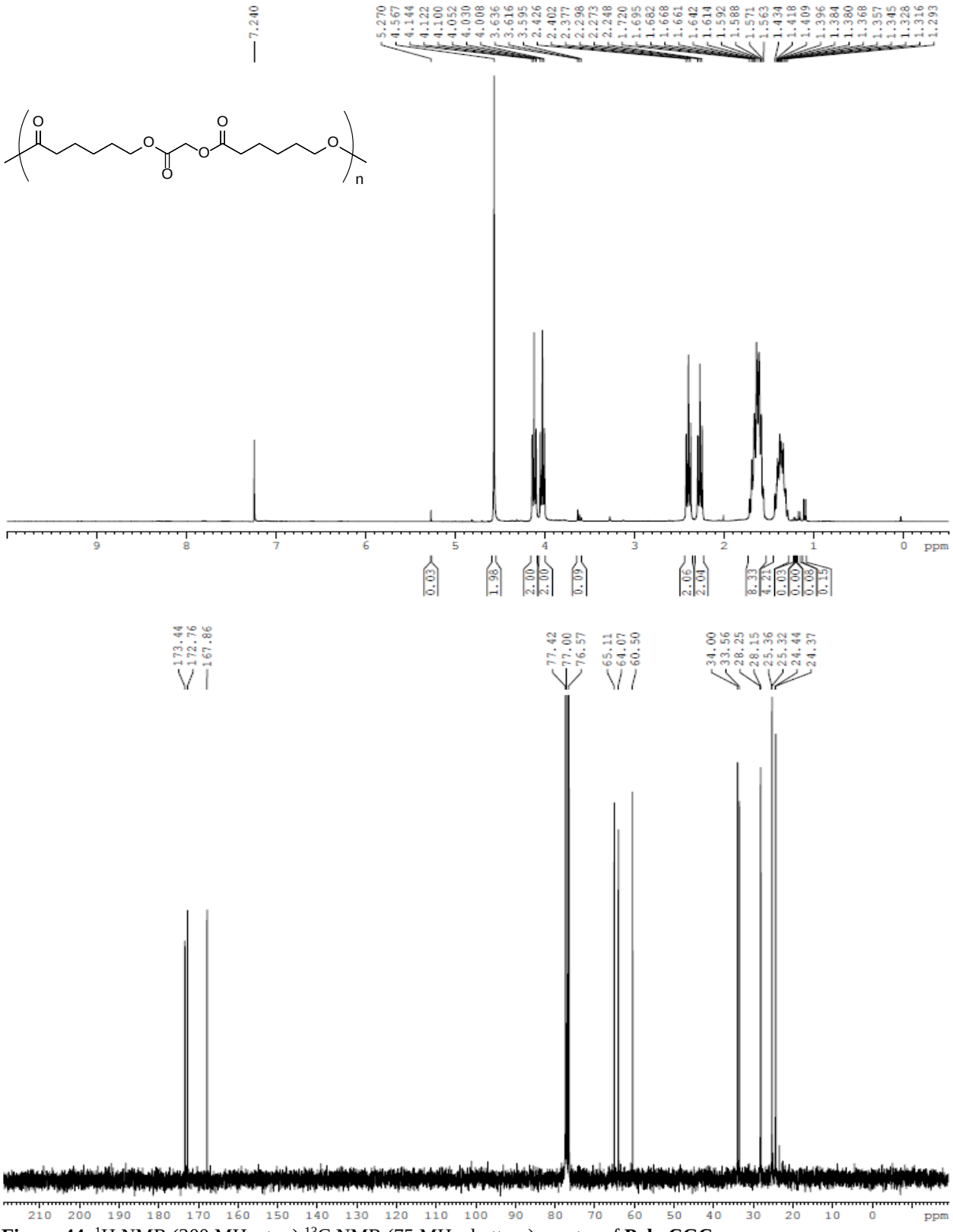


Figure 44. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly CGC**.

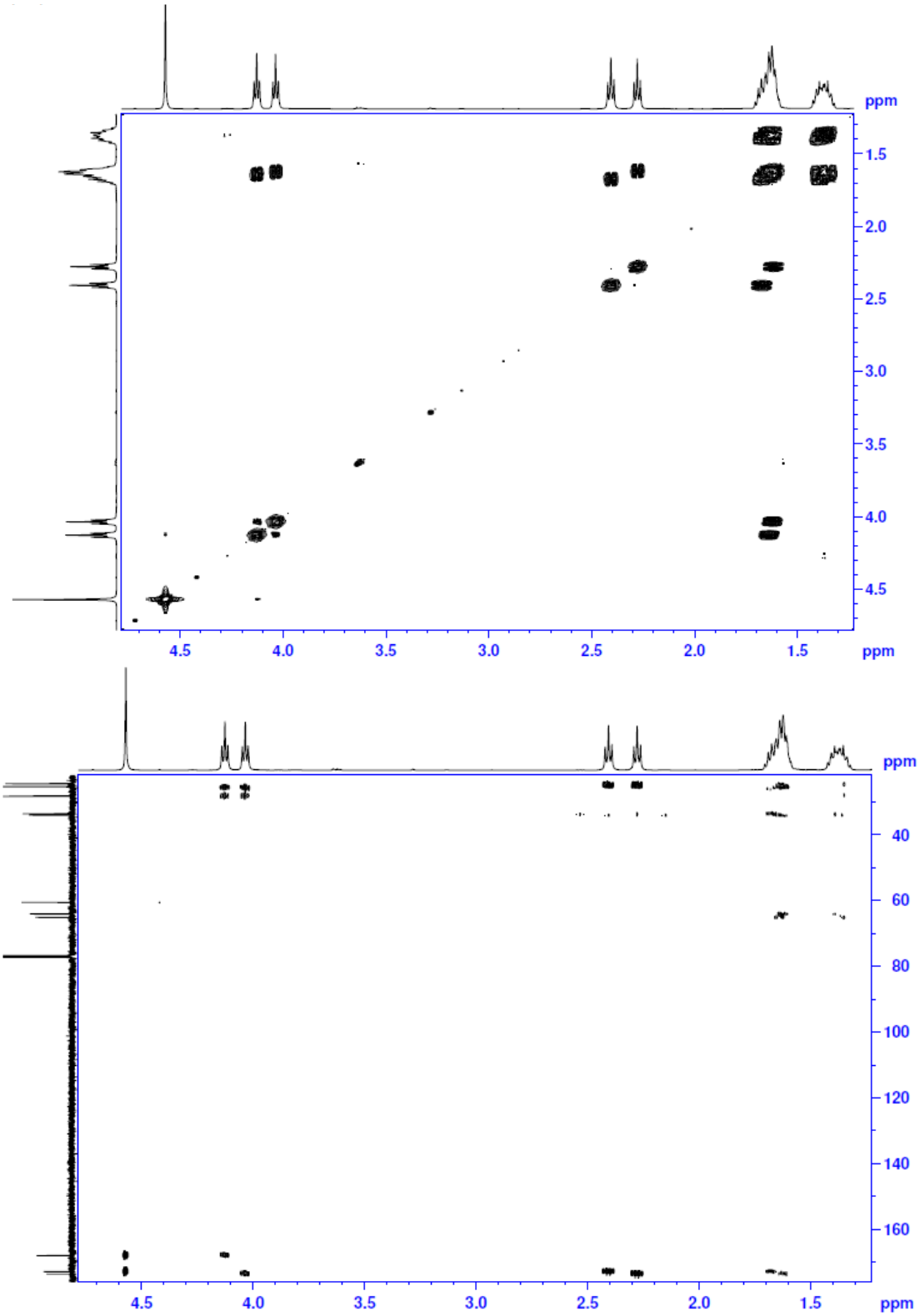


Figure 45. 2D COSY NMR (500 MHz, top) and 2D HMBC NMR (500 -125 MHz, bottom) spectra of **Poly CGC**.

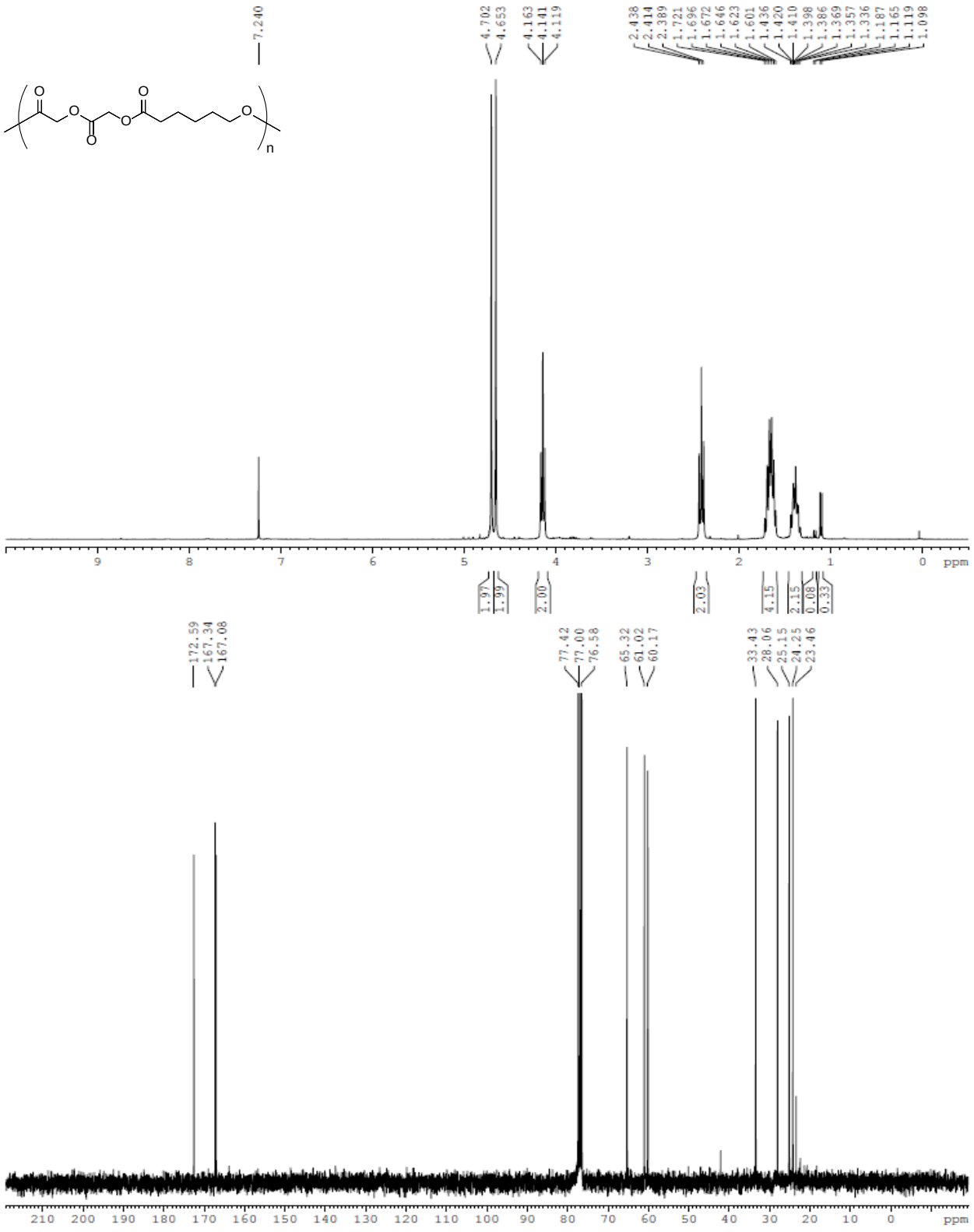


Figure 46. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly GGC**.

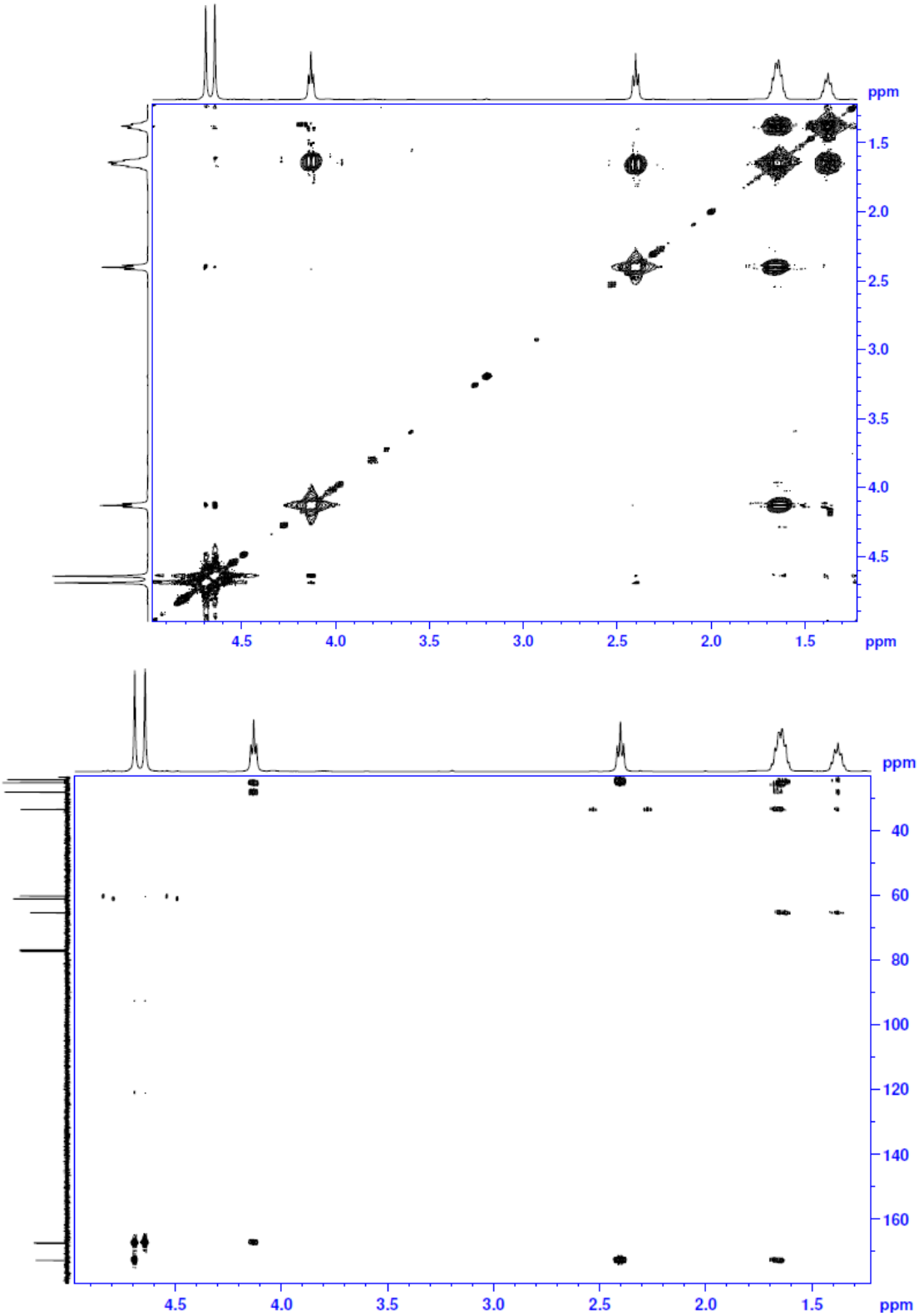


Figure 47. 2D COSY NMR (500 MHz, top) and 2D HMBC NMR (500 - 125 MHz, bottom) spectra of **Poly GGC**.

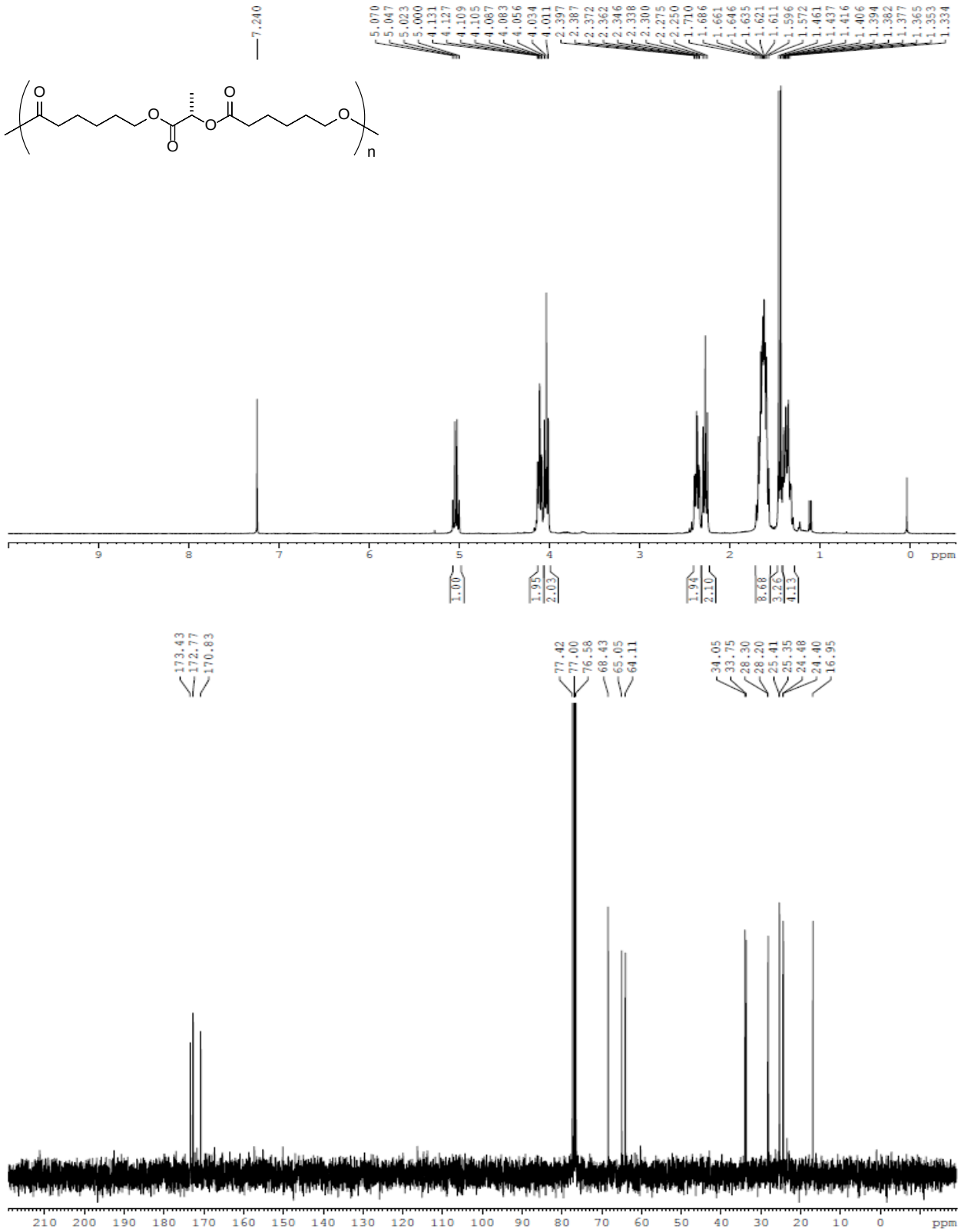


Figure 48. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly CLC**.

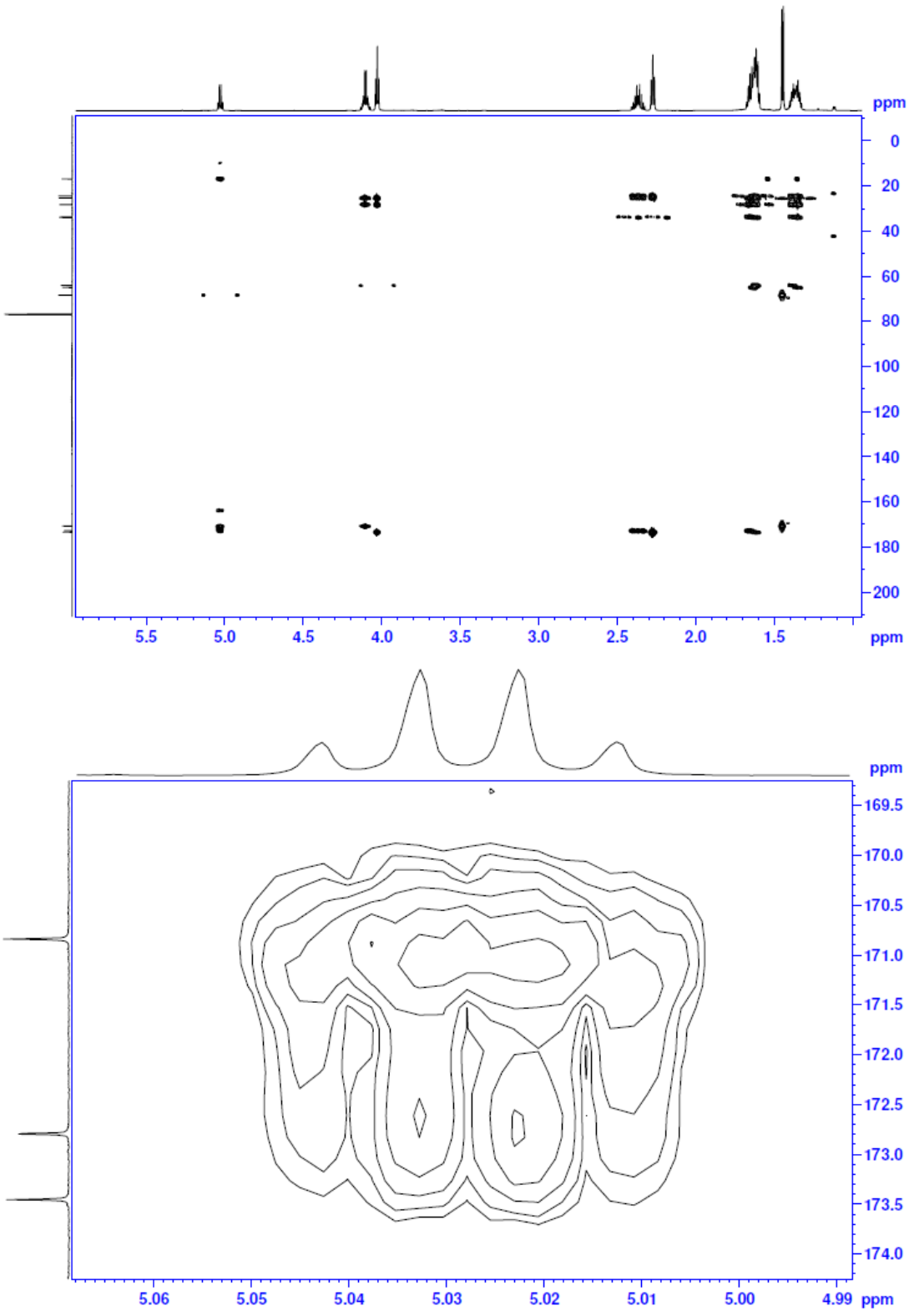


Figure 49. 2D HMBC NMR (700 – 175 MHz, top) and expansion (bottom) spectrum of **Poly CLC**.

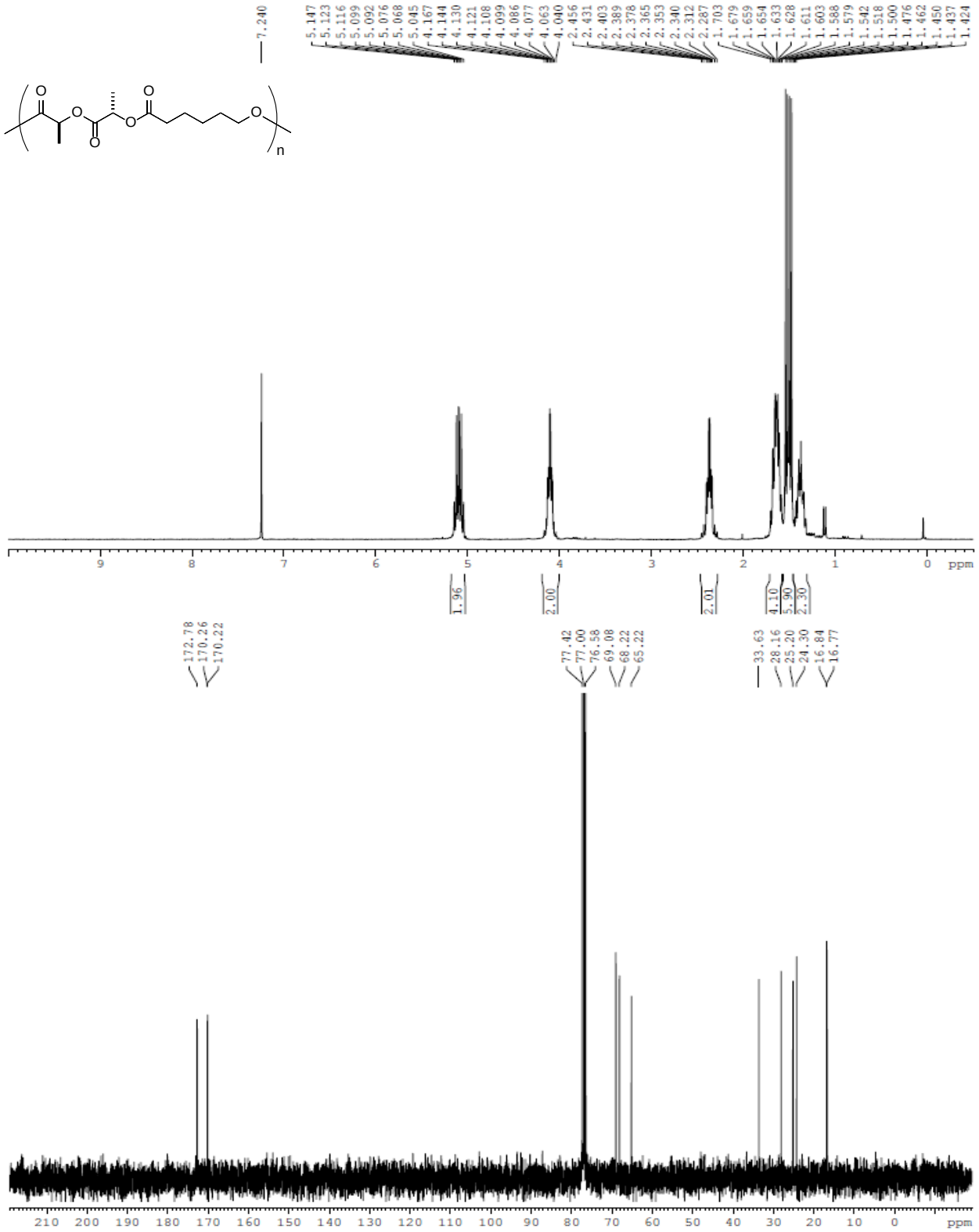


Figure 50. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LLC**.

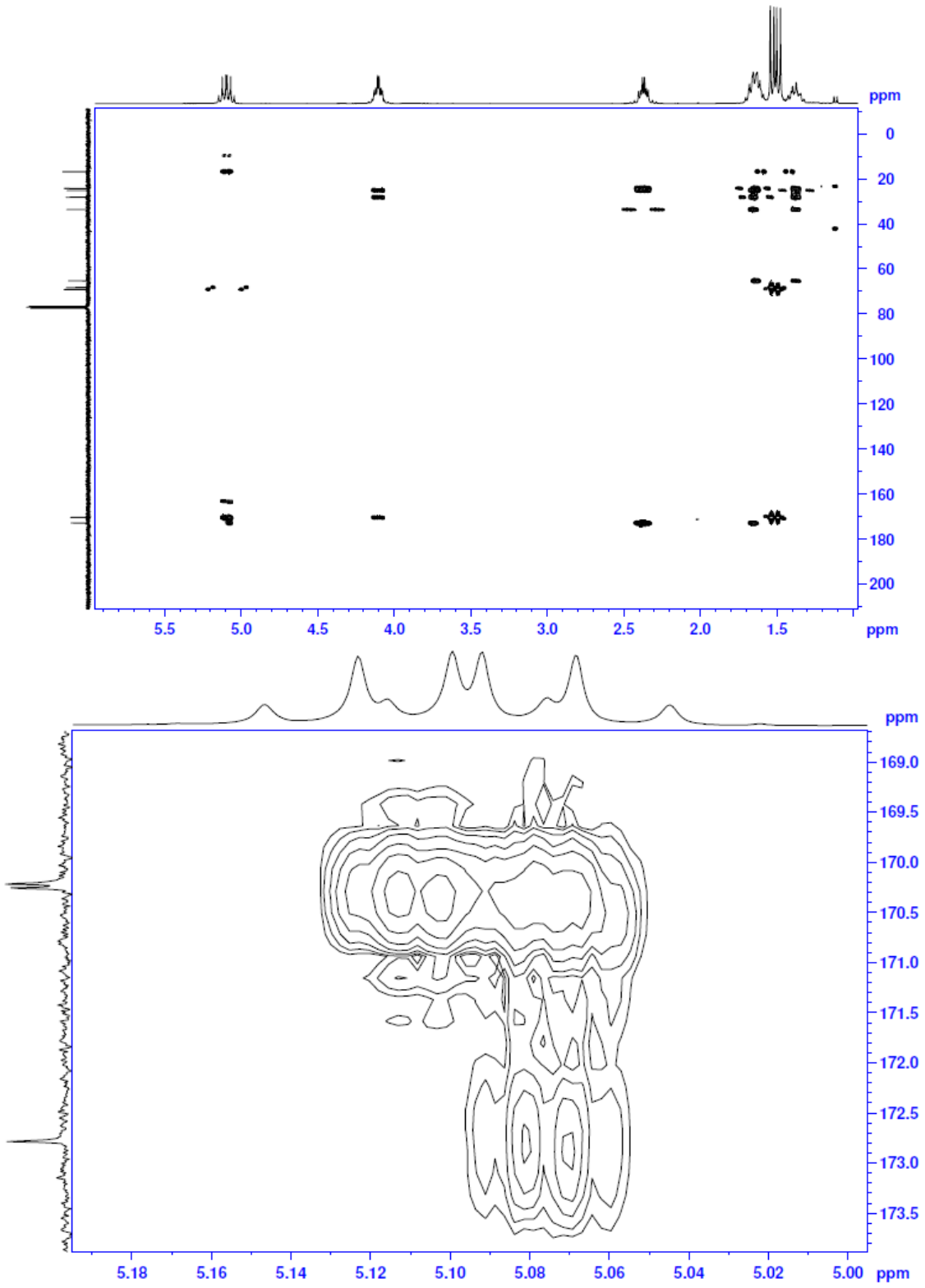


Figure 51. 2D HMBC NMR (700 – 175 MHz, top) and expansion (bottom) spectrum of **Poly LLC**.

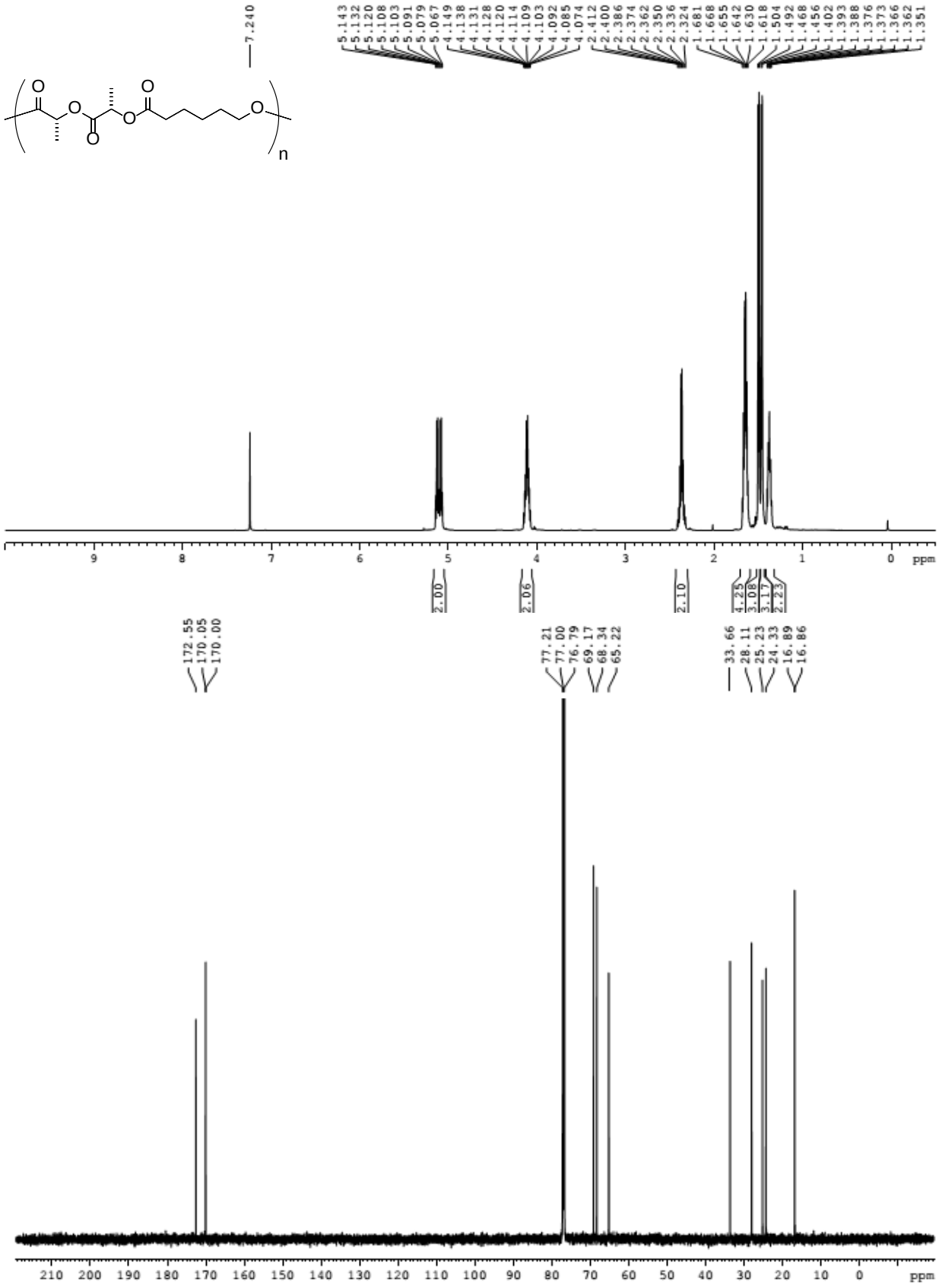


Figure 52. ^{1}H NMR (600 MHz, top) ^{13}C NMR (150 MHz, bottom) spectra of **Poly L$_{R}$LC**.

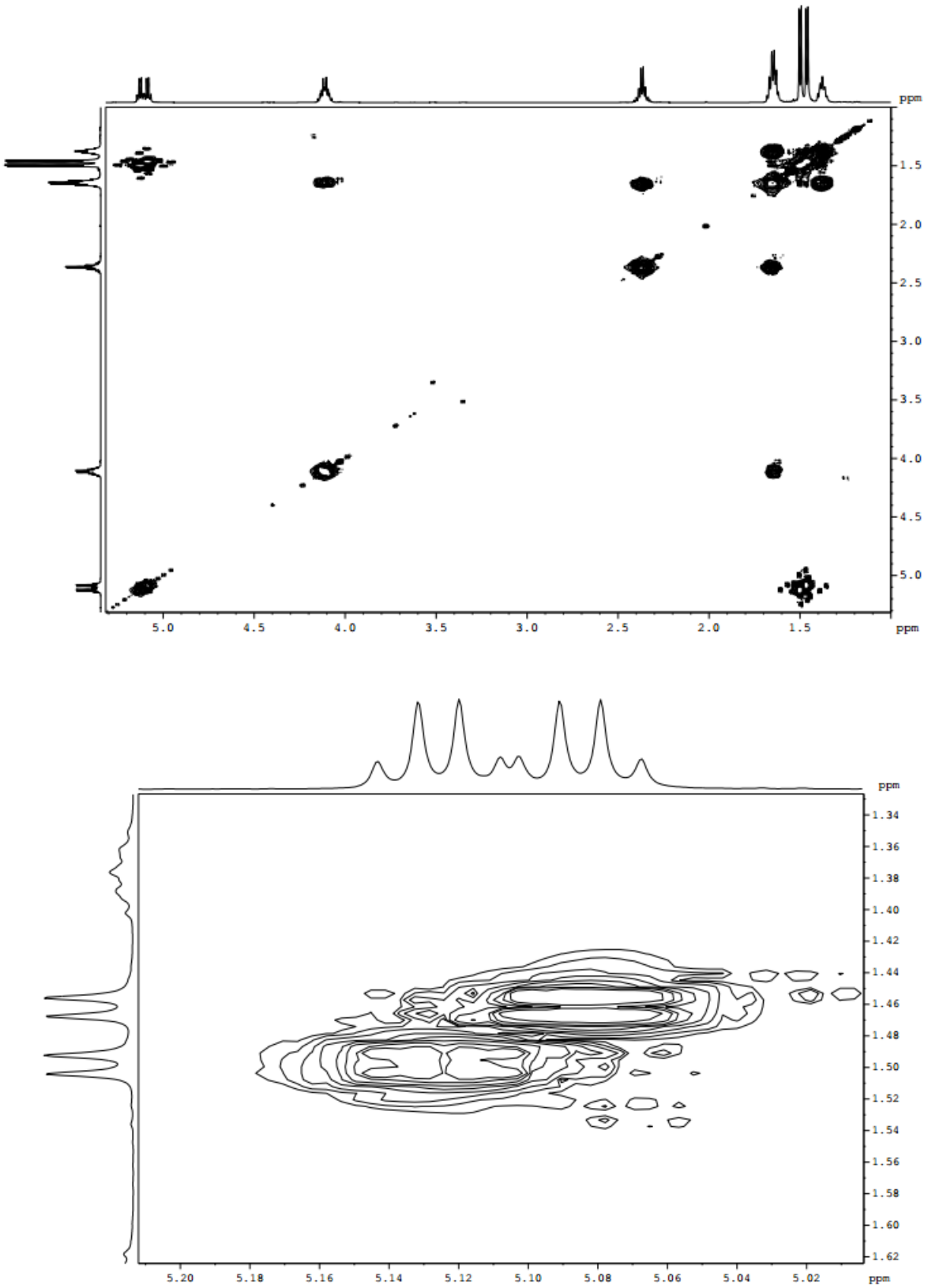


Figure 53. 2D COSY NMR (600 MHz, top) and expansion (bottom) spectrum of **Poly L_RLC**.

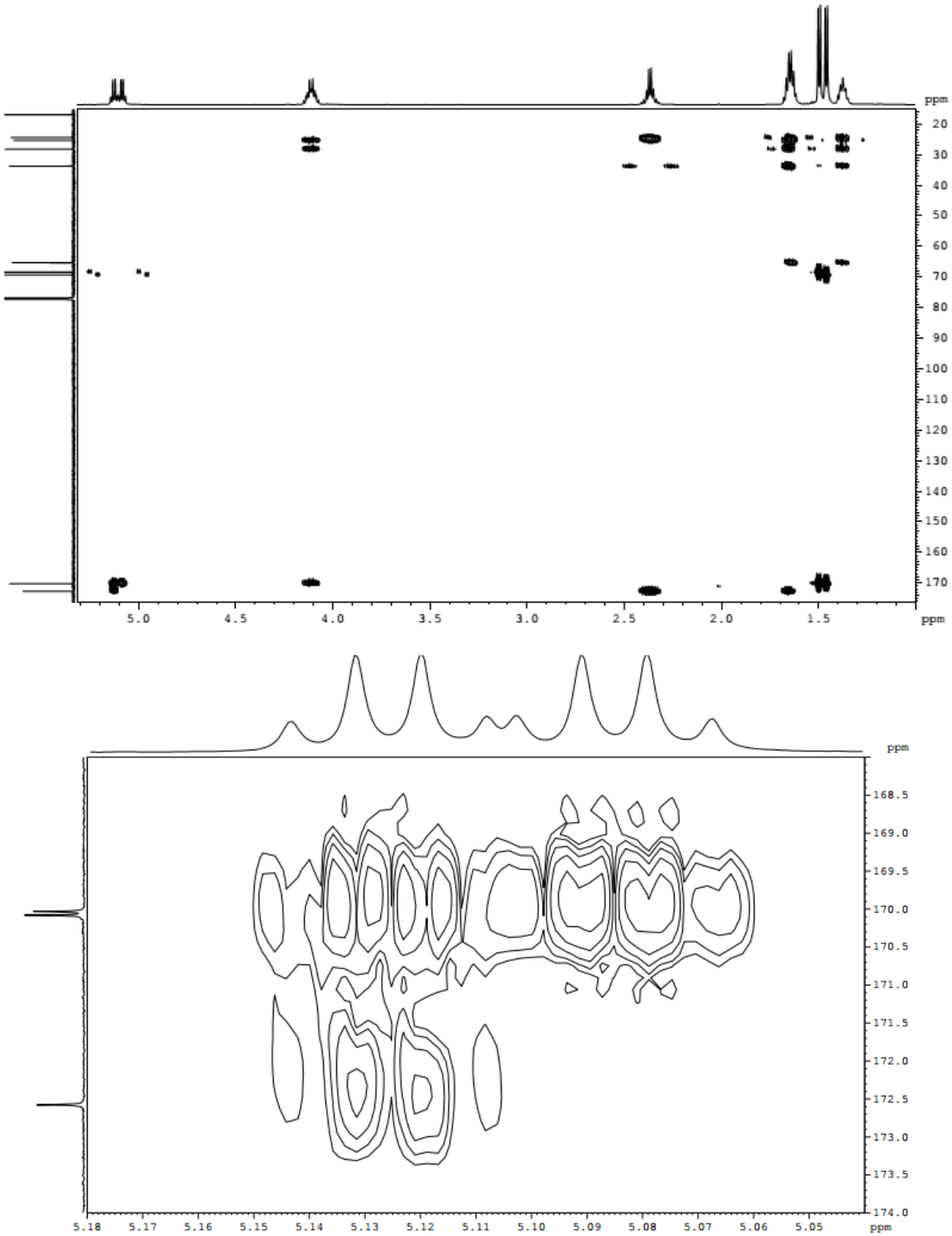


Figure 54. 2D HMBC NMR (600 – 150 MHz, top) and expansion (bottom) spectrum of **Poly L_RLC**.

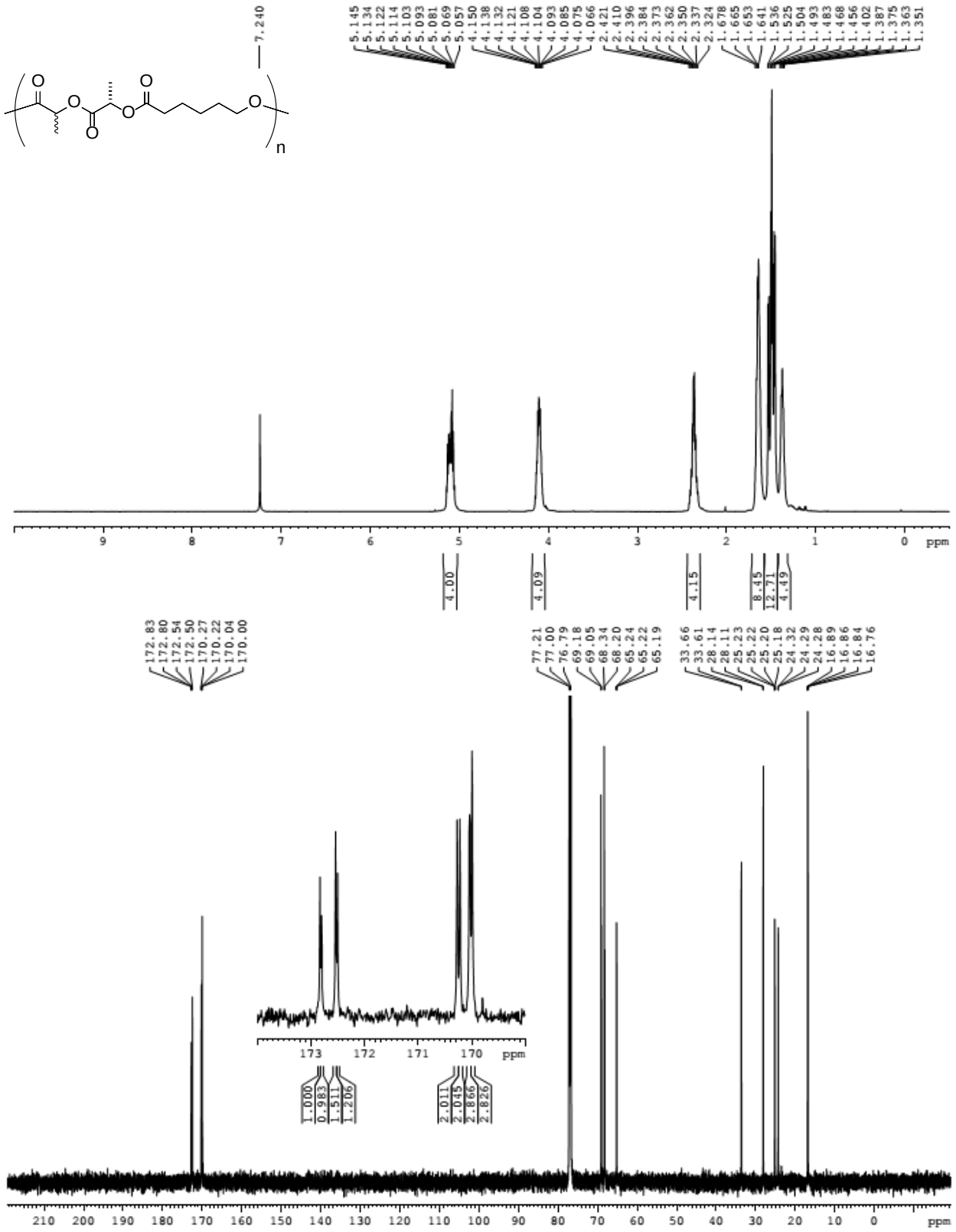


Figure 55. ^{1}H NMR (600 MHz, top) ^{13}C NMR (150 MHz, bottom) spectra of **Poly L$_{rac}$LC**.

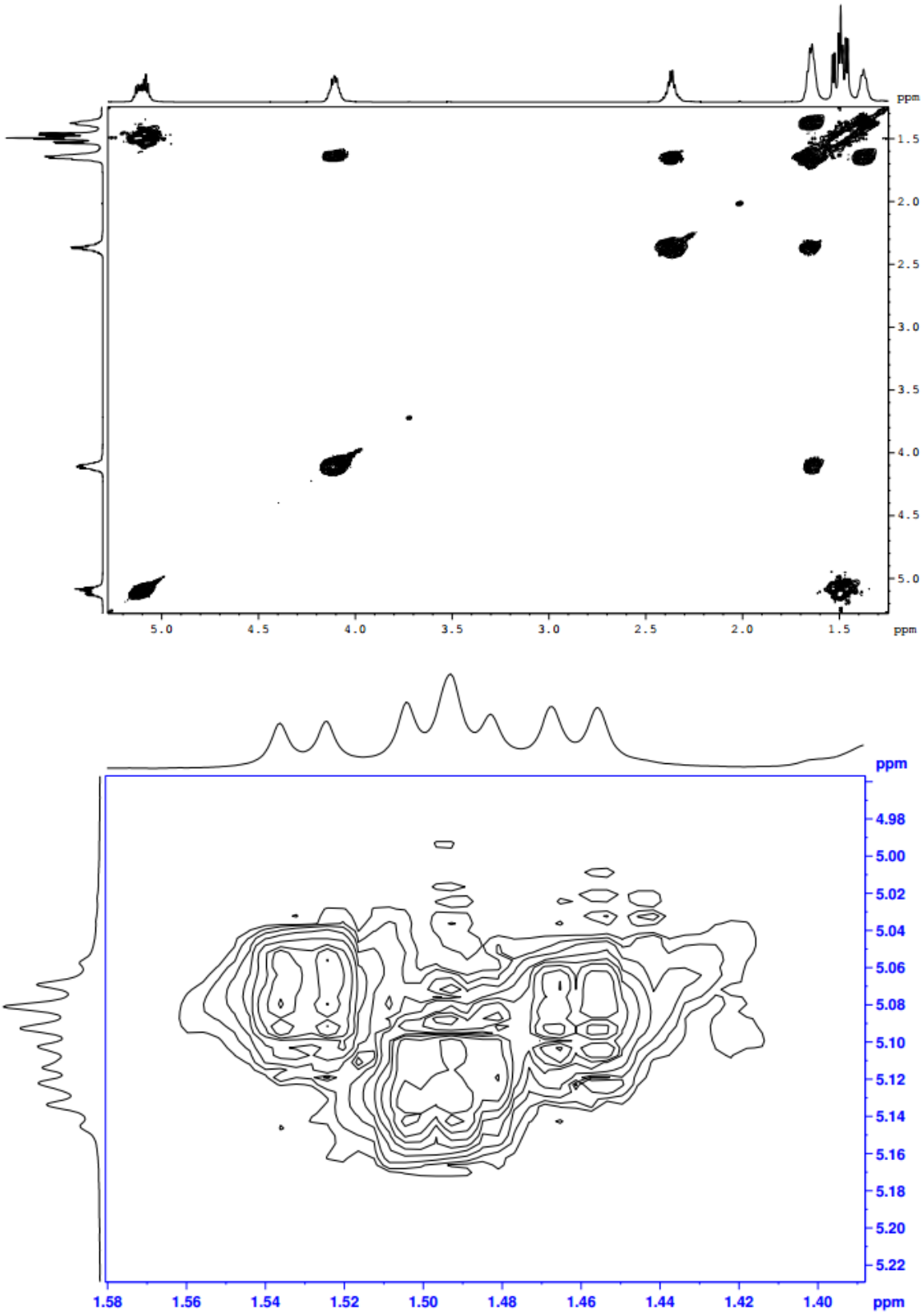


Figure 56. 2D COSY NMR (600 MHz, top) spectrum and expansion (bottom) of **Poly L_{rac}LC**.

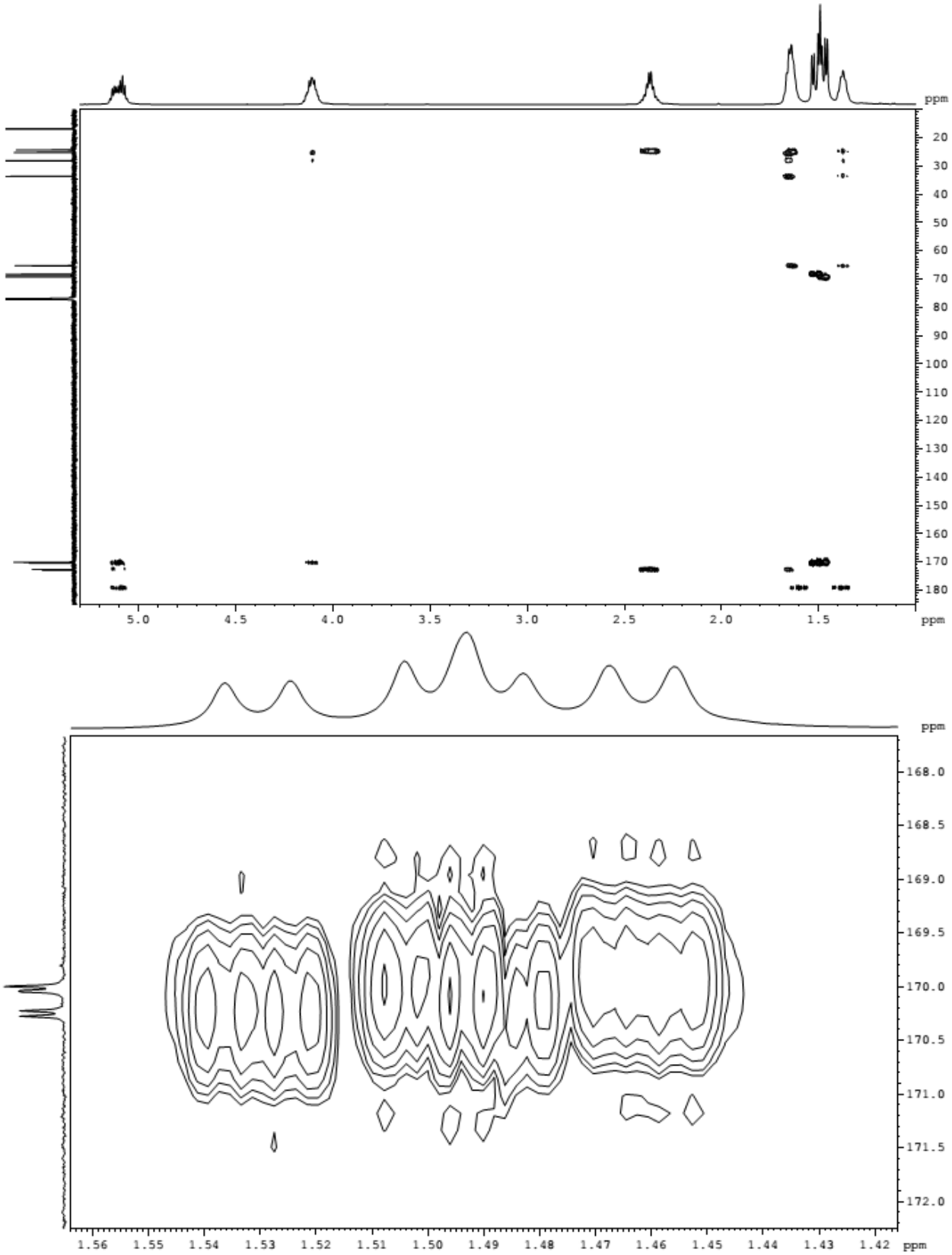


Figure 57. 2D HMBC NMR (600 – 150 MHz, top) spectrum and expansion (bottom) of **Poly L$_{rac}$LC**.

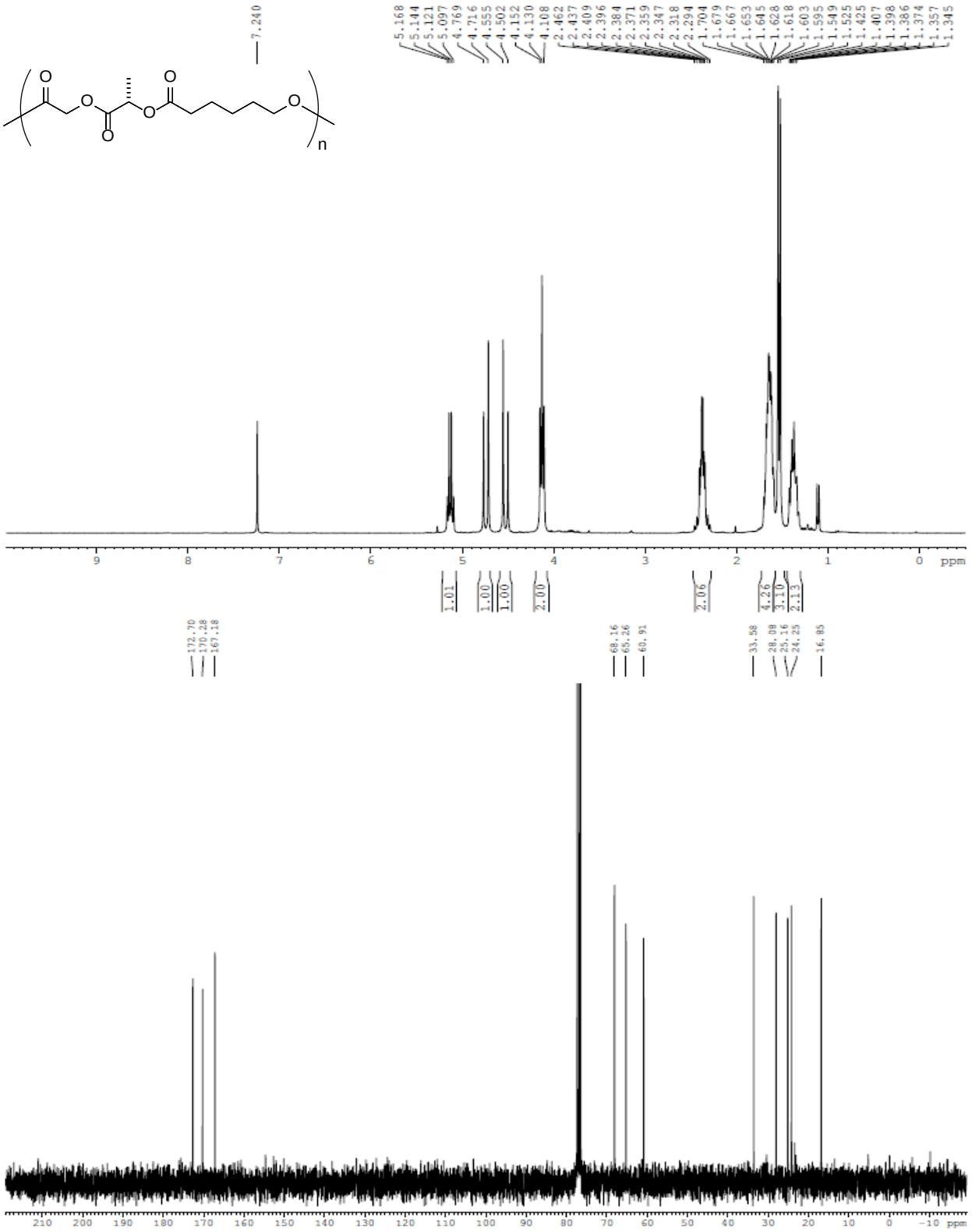


Figure 58. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly GLC**.

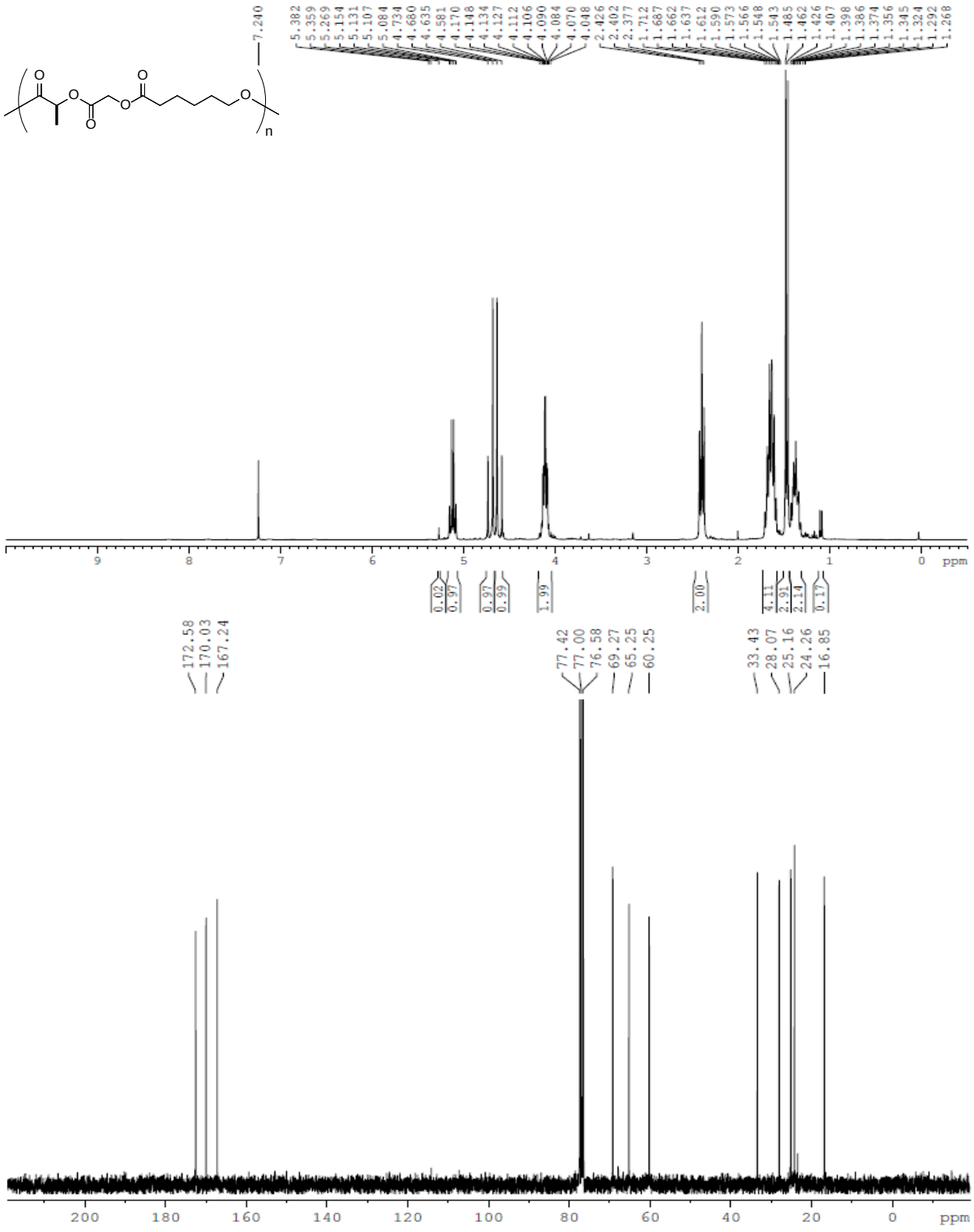


Figure 59. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LGC**.

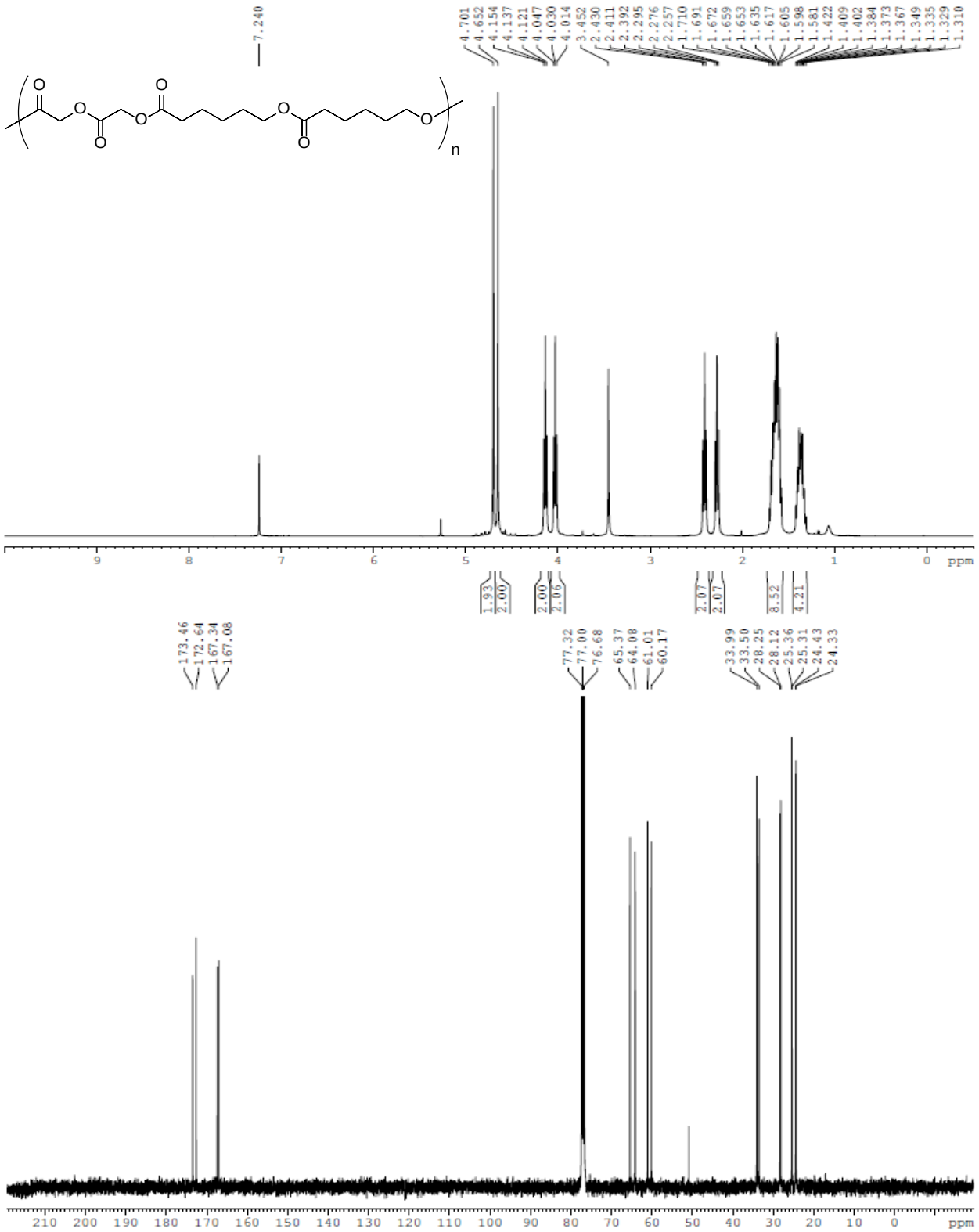


Figure 60. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly GGCC**.

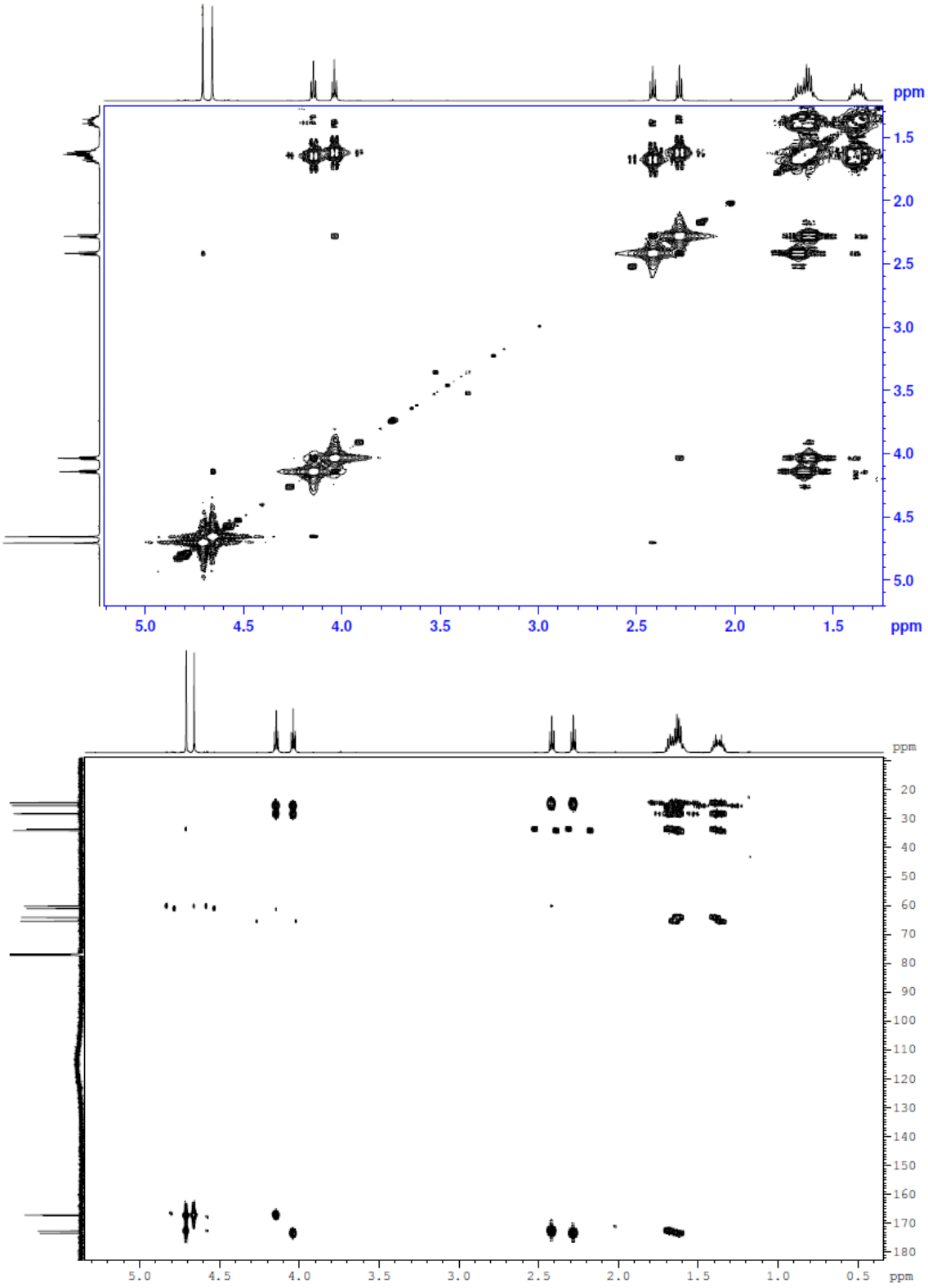


Figure 61. 2D COSY NMR (600 MHz, top) and 2D HMBC NMR (600 - 150 MHz, bottom) spectra of **Poly GGC**.

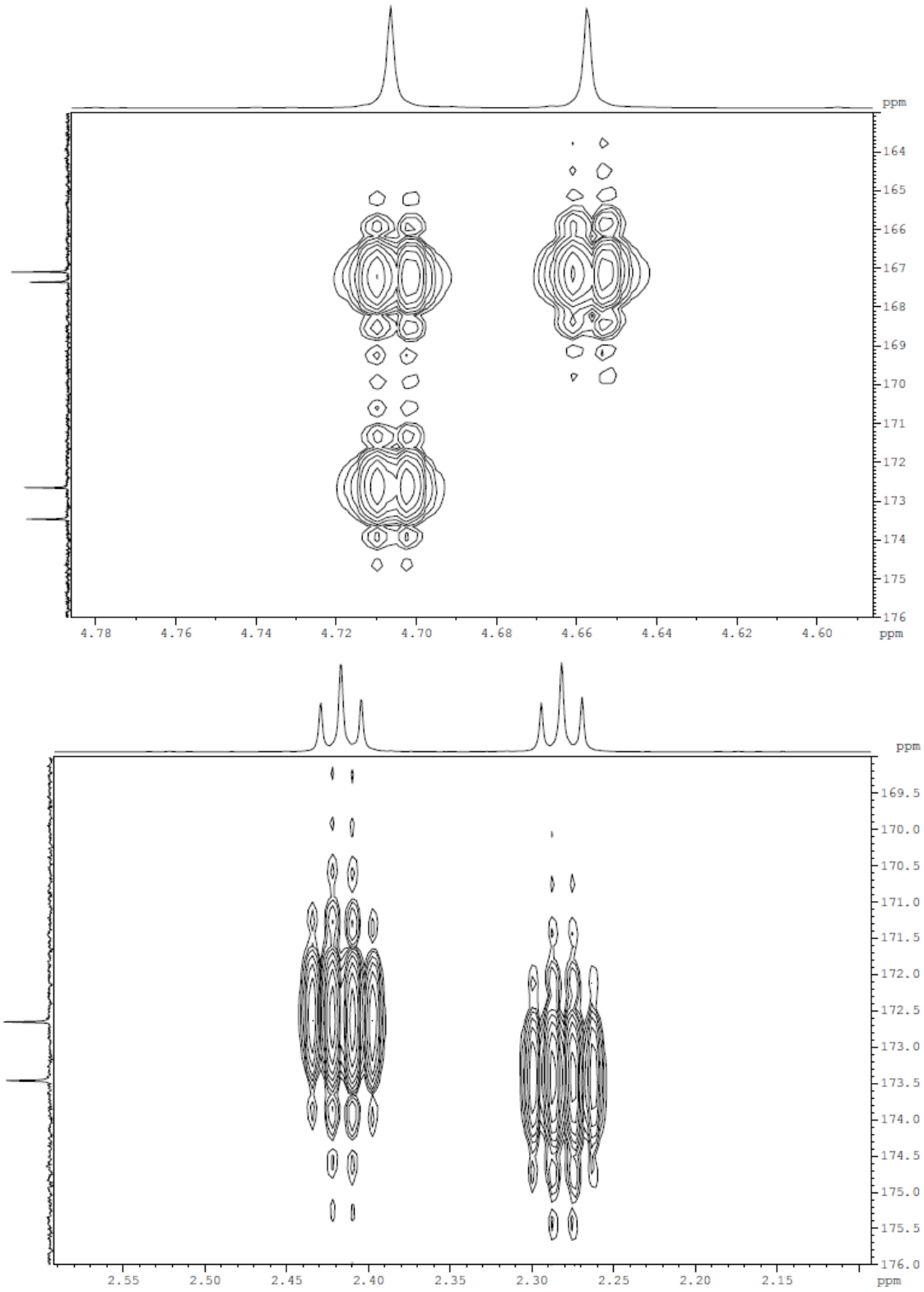


Figure 62. Expansions of 2D HMBC NMR (600 – 150 MHz, $CDCl_3$, 25 ºC) spectrum of **Poly GGCC**.

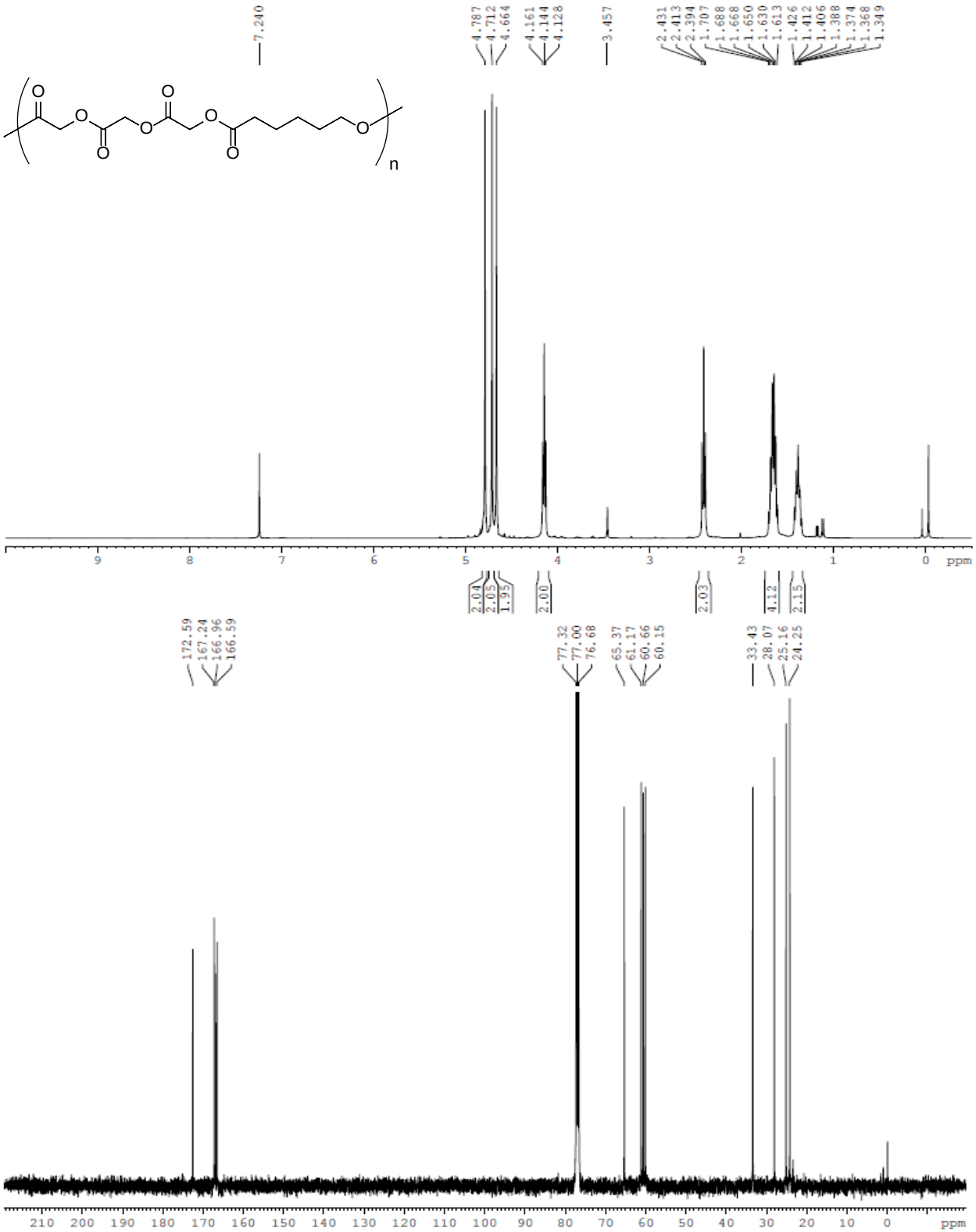


Figure 63. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly GGGC**.

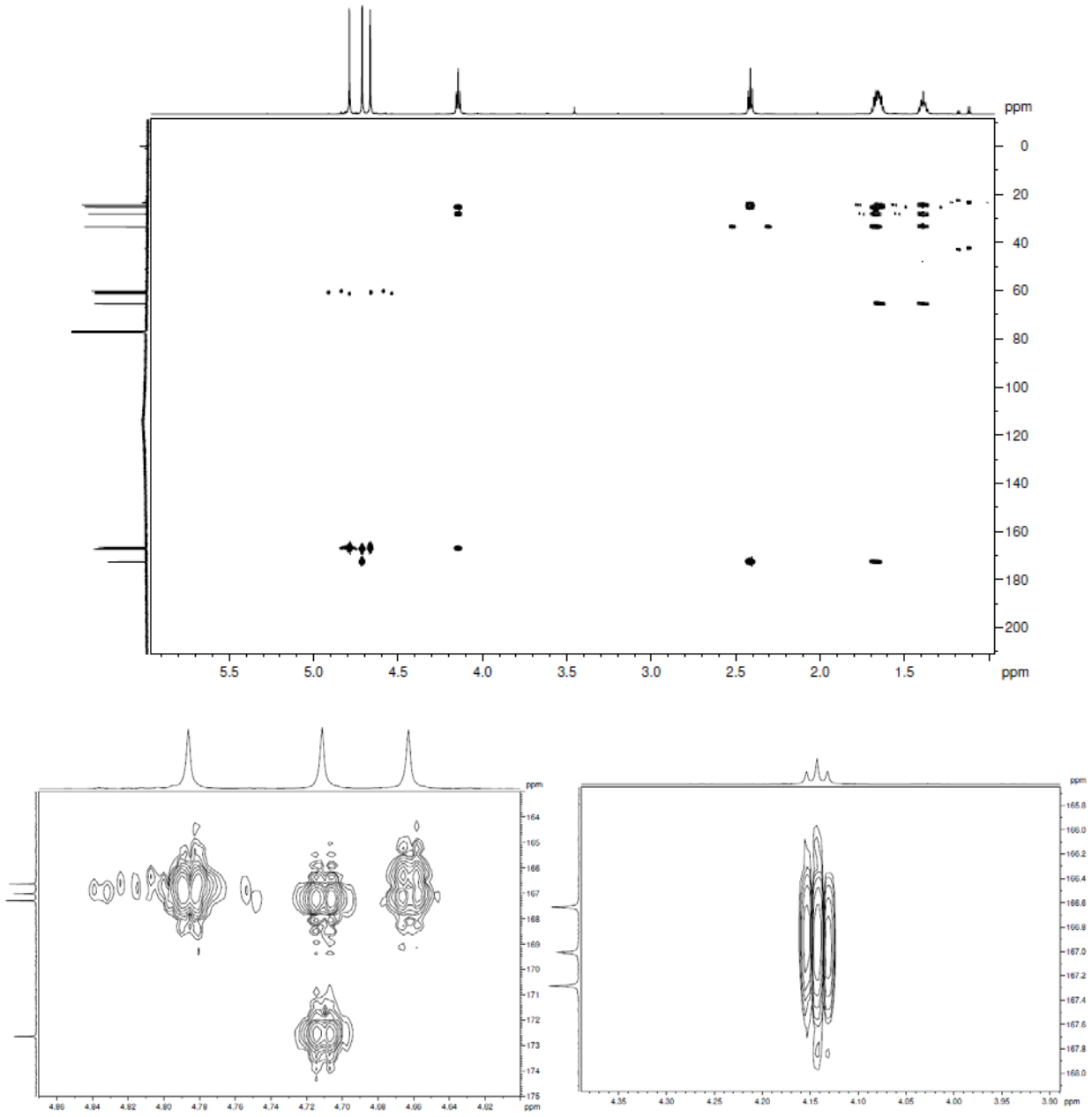


Figure 64. 2D HMBC NMR (600 - 150 MHz, top) spectrum and expansions (bottom left and right) of **Poly GGC**.

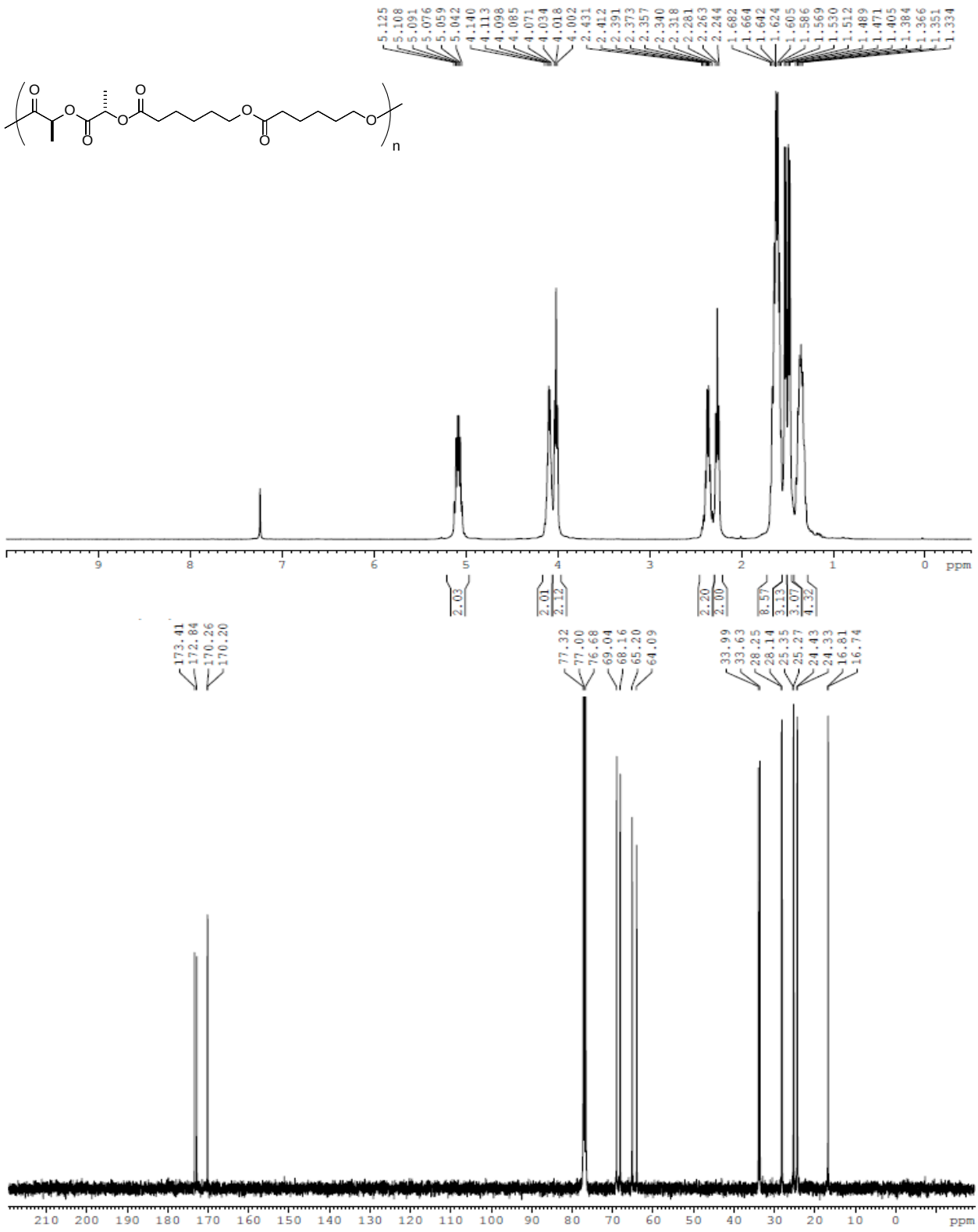


Figure 65. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly LLCC**.

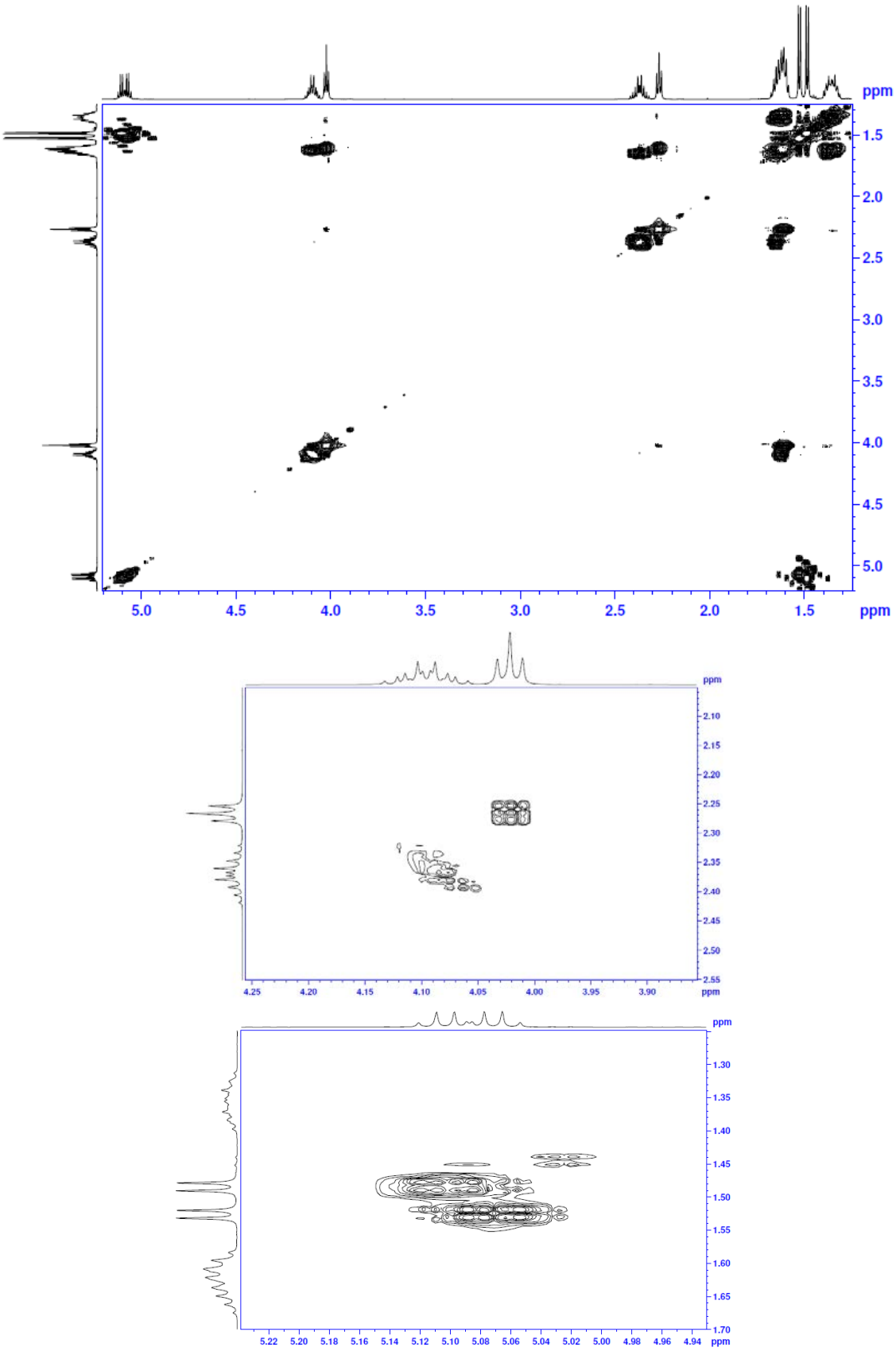


Figure 66. 2D COSY NMR (600 MHz, top) spectrum and expansions (bottom middle and bottom) of **Poly LLCC**.

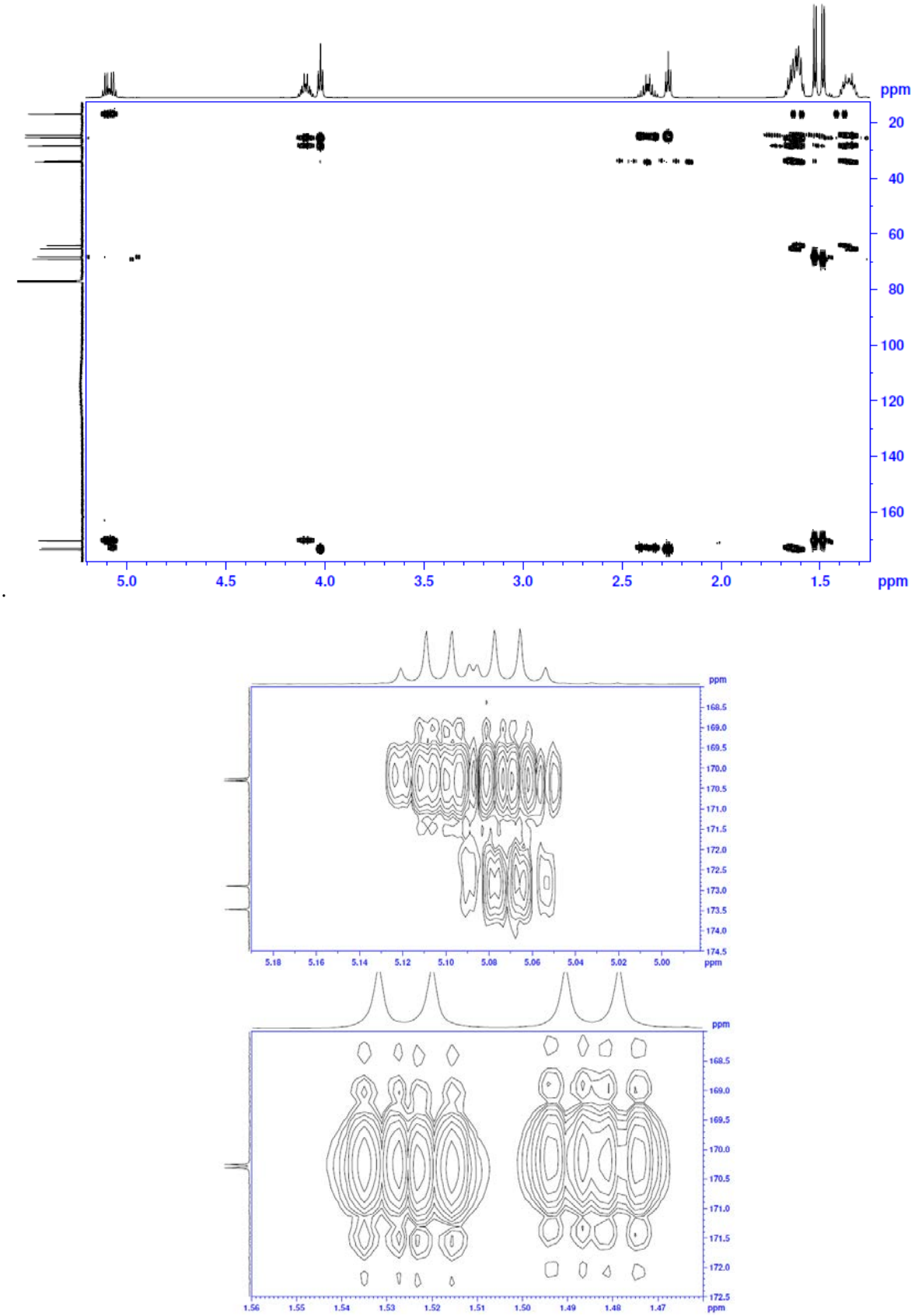


Figure 67. 2D HMBC NMR (600 – 150 MHz, top) spectrum and expansions (middle and bottom) of **Poly LLCC**.

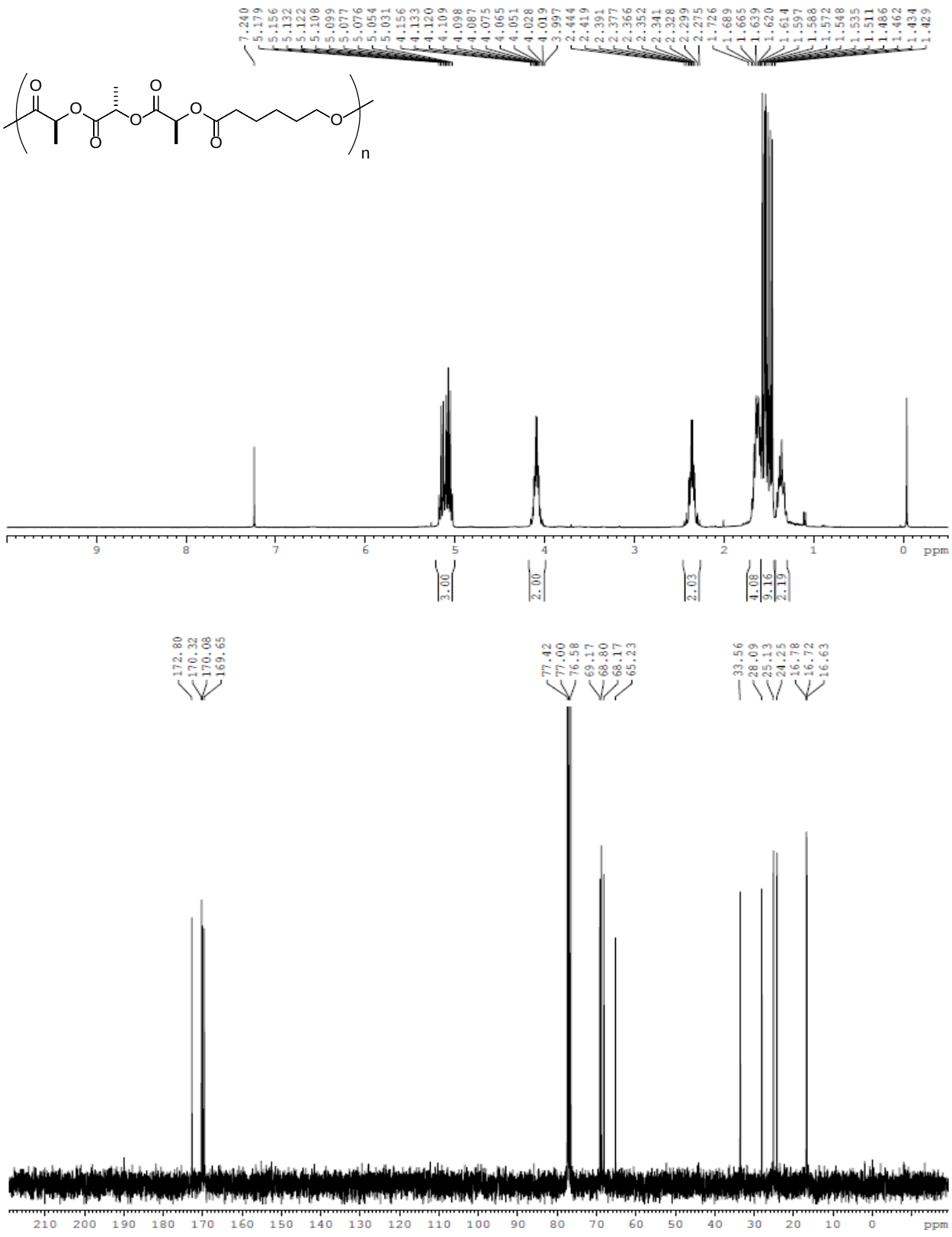


Figure 68. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LLLC**.

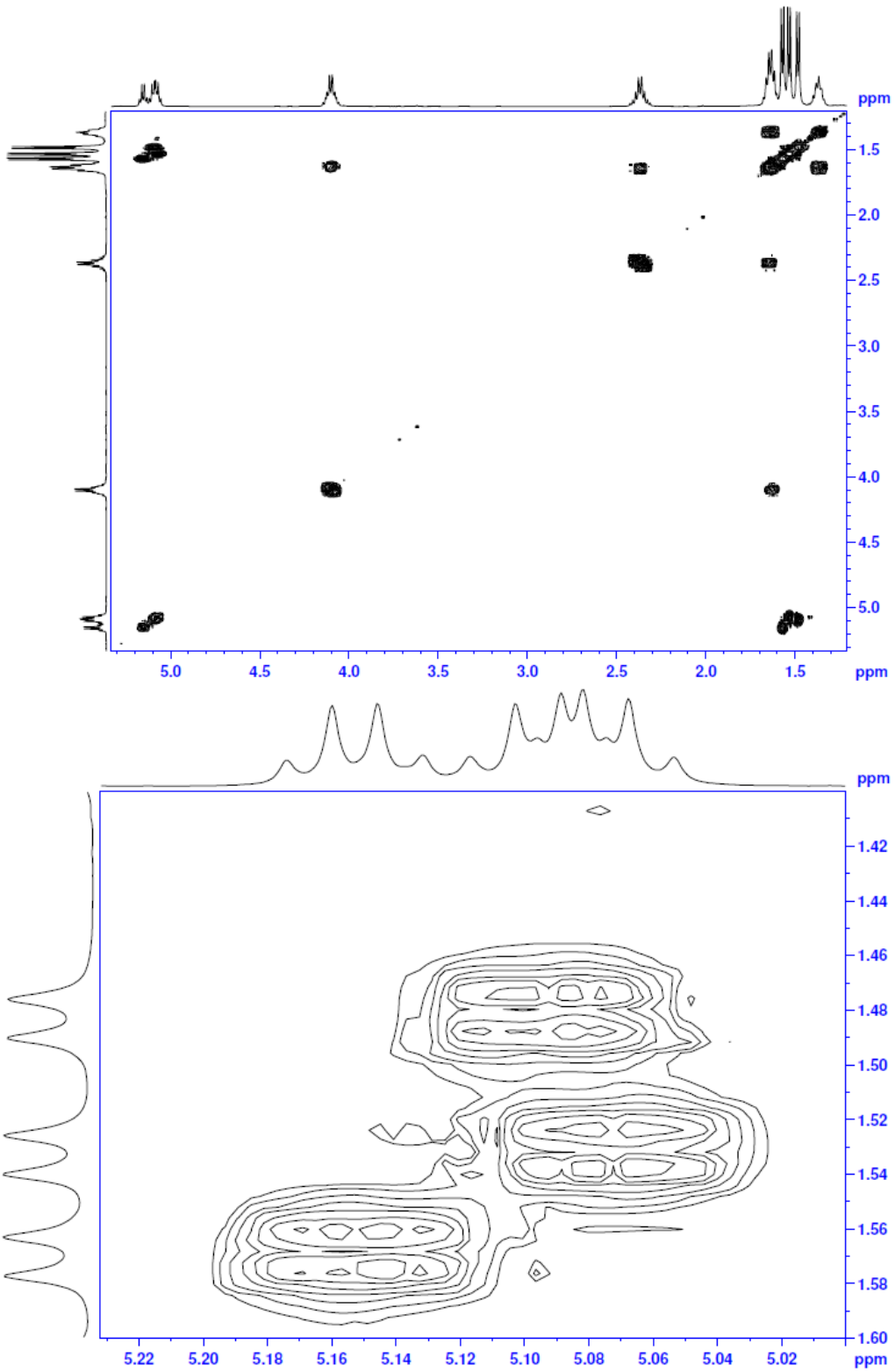


Figure 69. 2D COSY NMR (500 MHz, top) spectrum and expansion (bottom) of **Poly LLLC**.

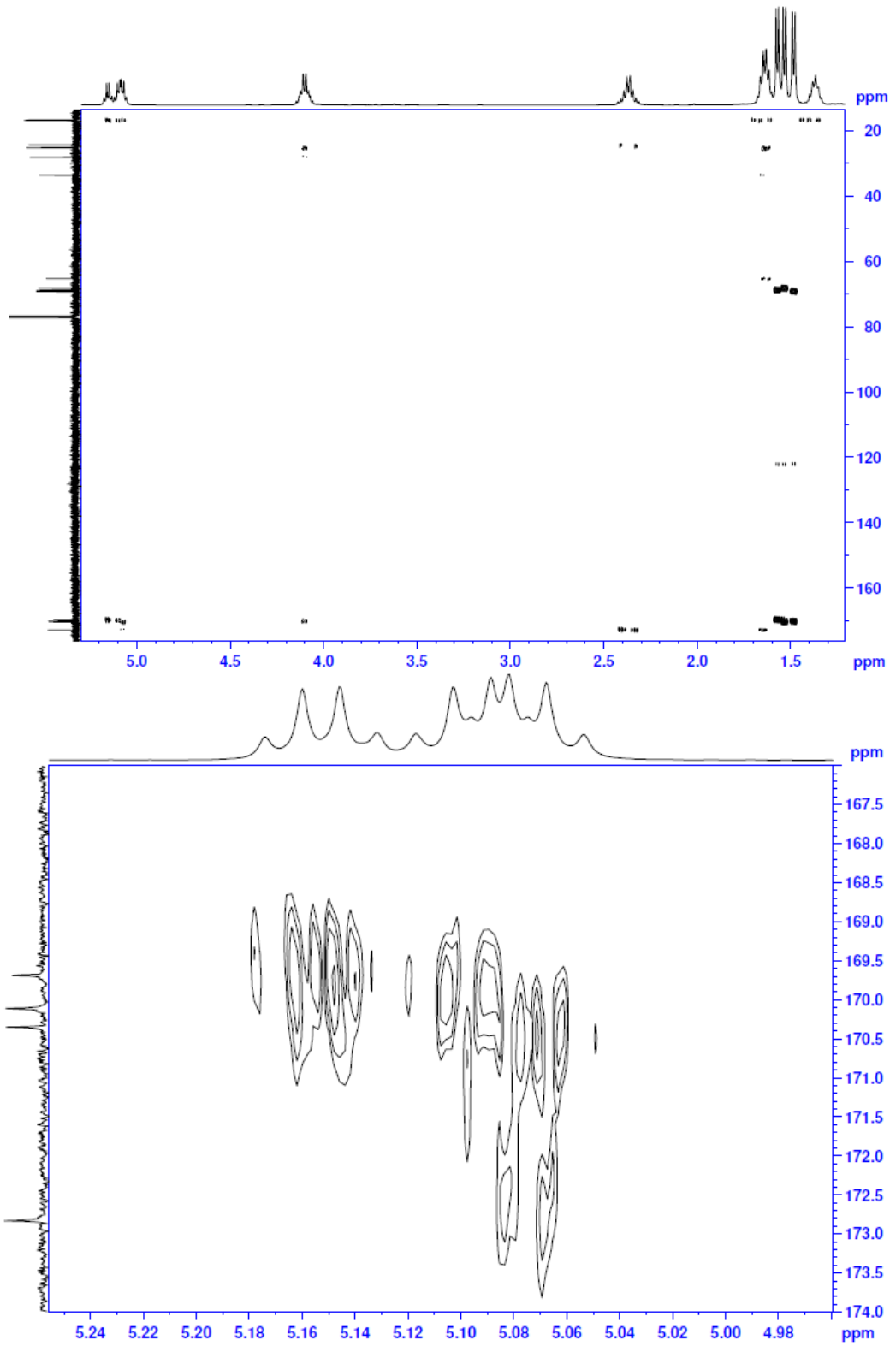


Figure 70. 2D HMBC NMR (500 – 125 MHz, top) spectrum and expansion (bottom) of **Poly LLLC**.

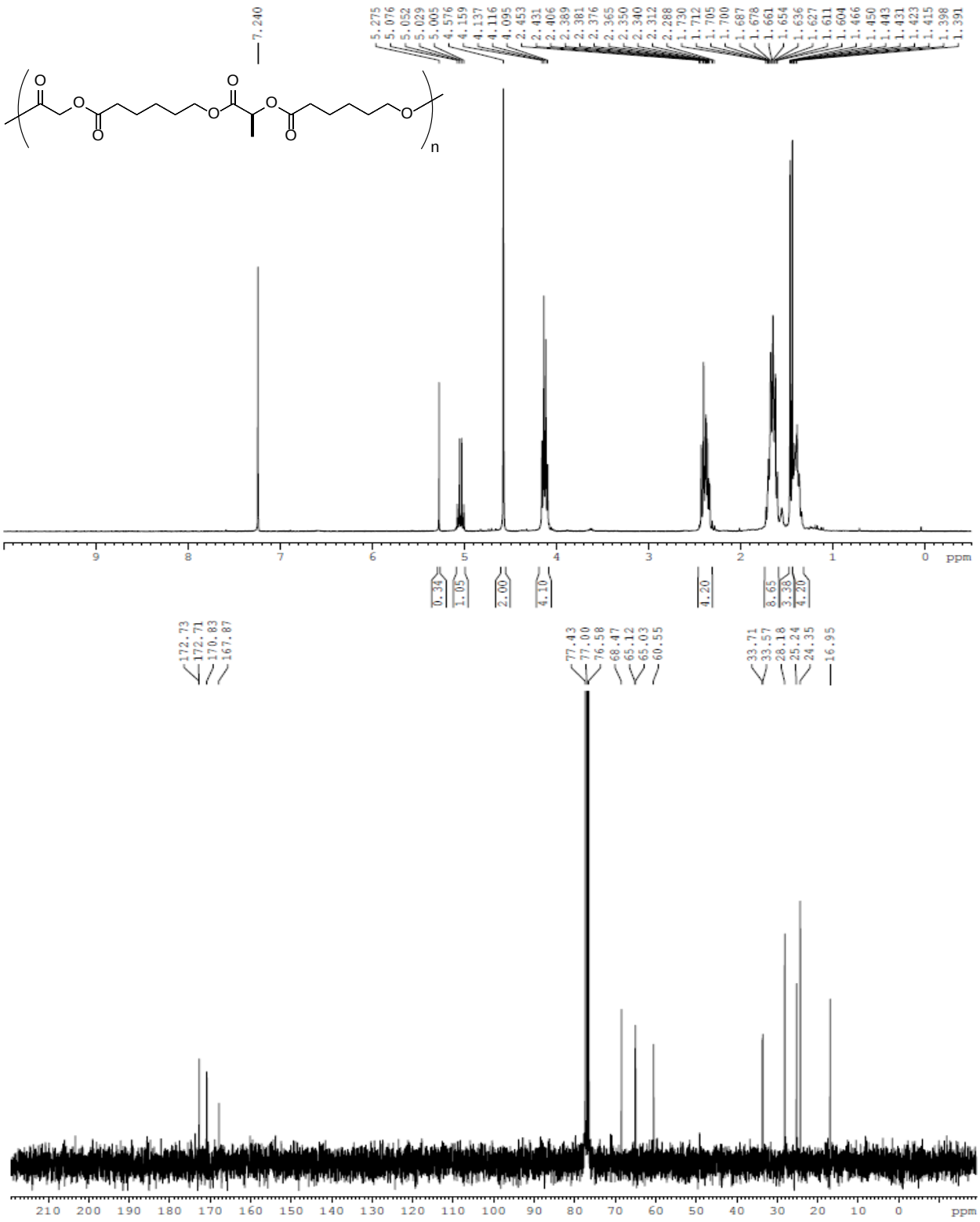


Figure 71. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly GCLC**.

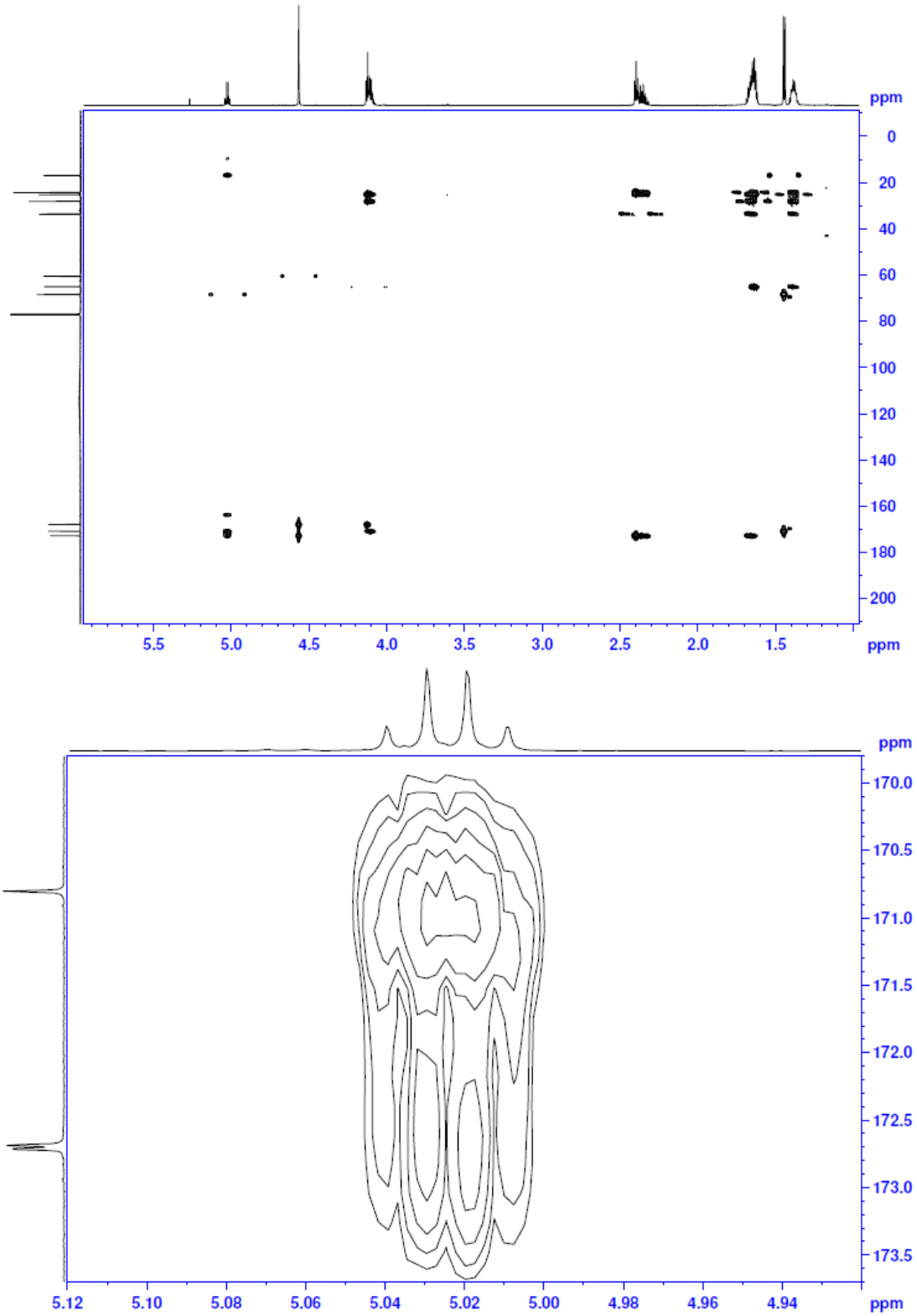


Figure 72. 2D HMBC NMR (700 – 175 MHz, top) and expansion (bottom) spectrum of **Poly GCLC**.

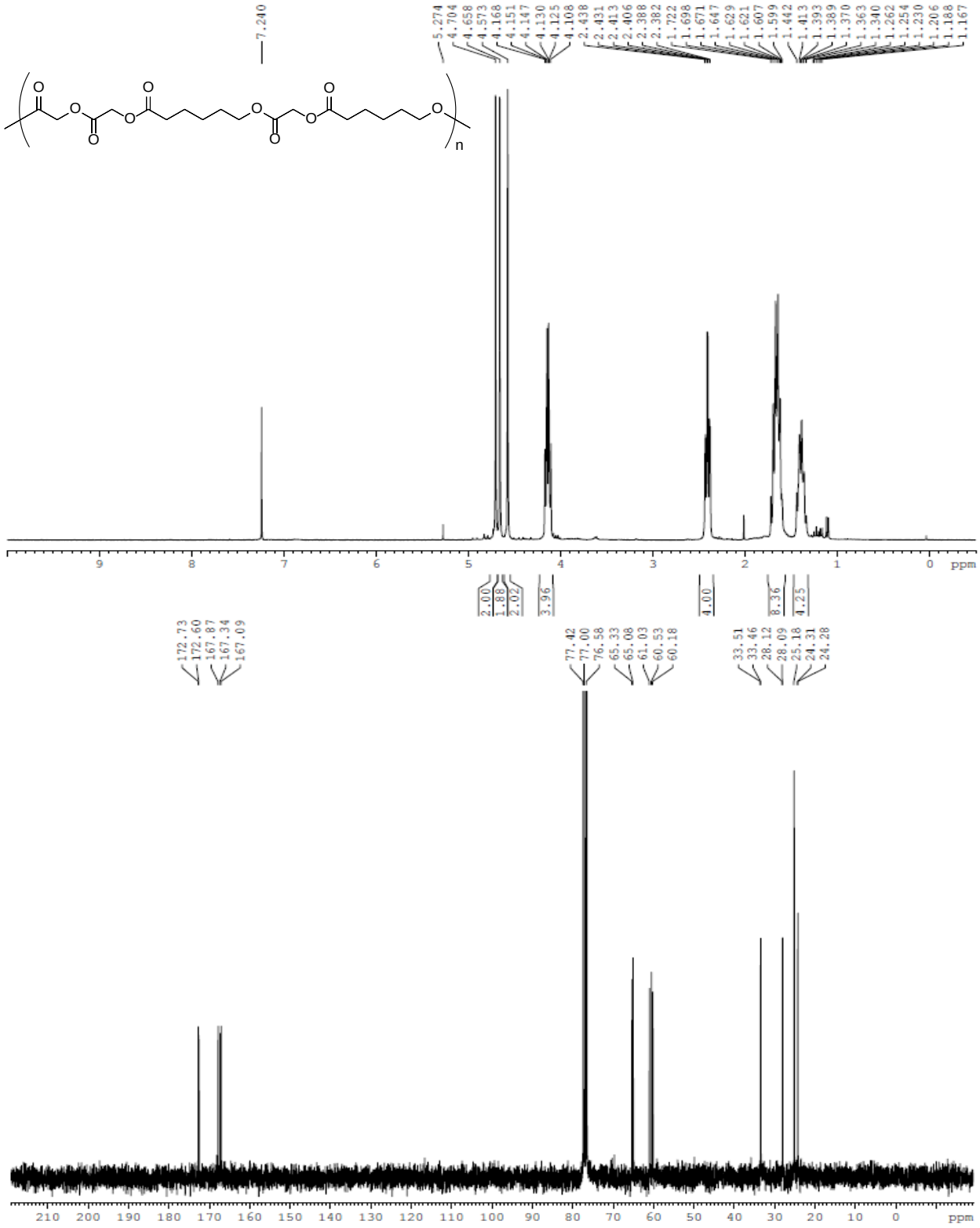


Figure 73. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly GGCGC**.

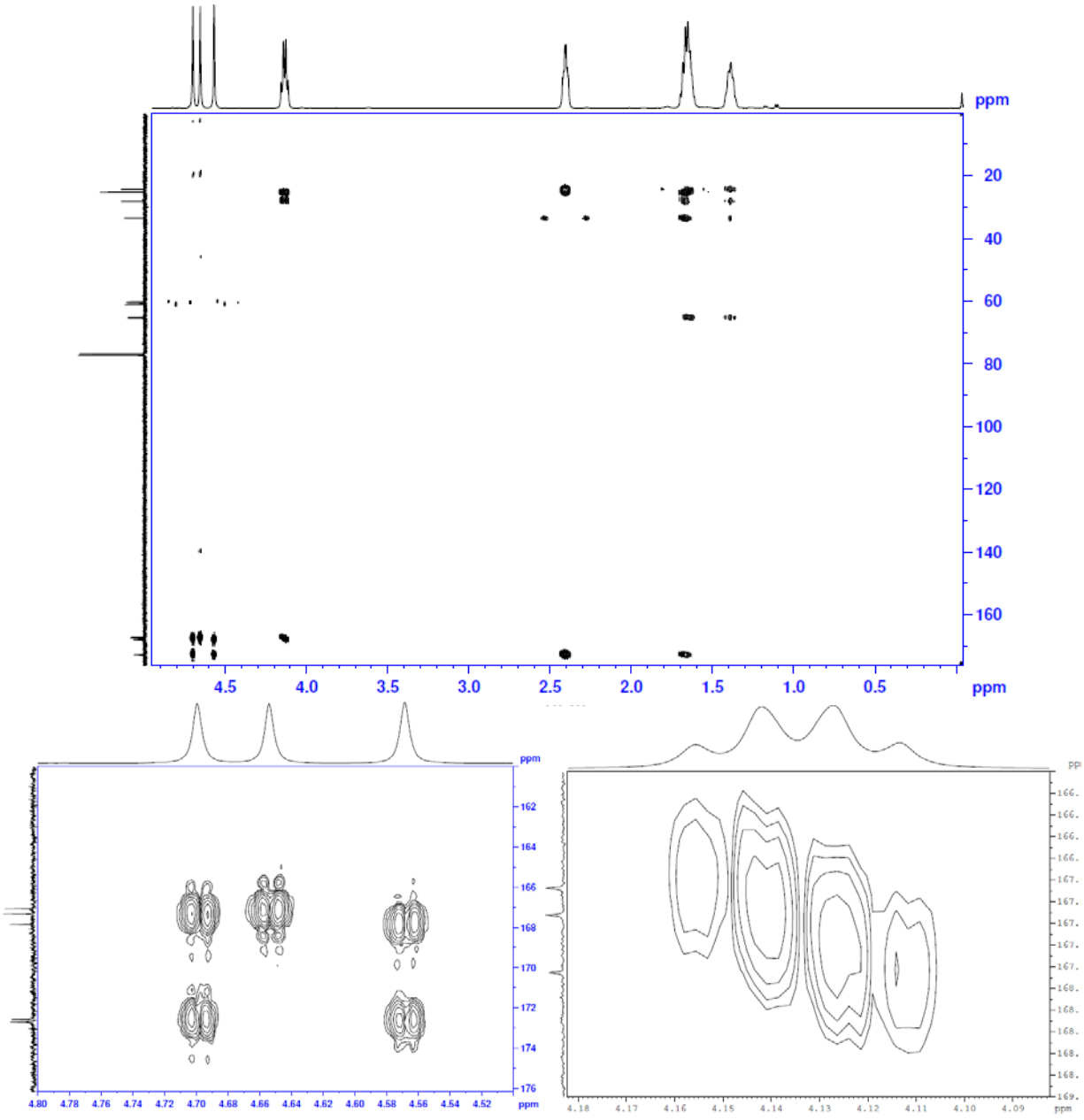


Figure 74. 2D HMBC NMR (700 – 175 MHz, top) spectrum and expansions (bottom left and right) of **Poly GGCGC**.

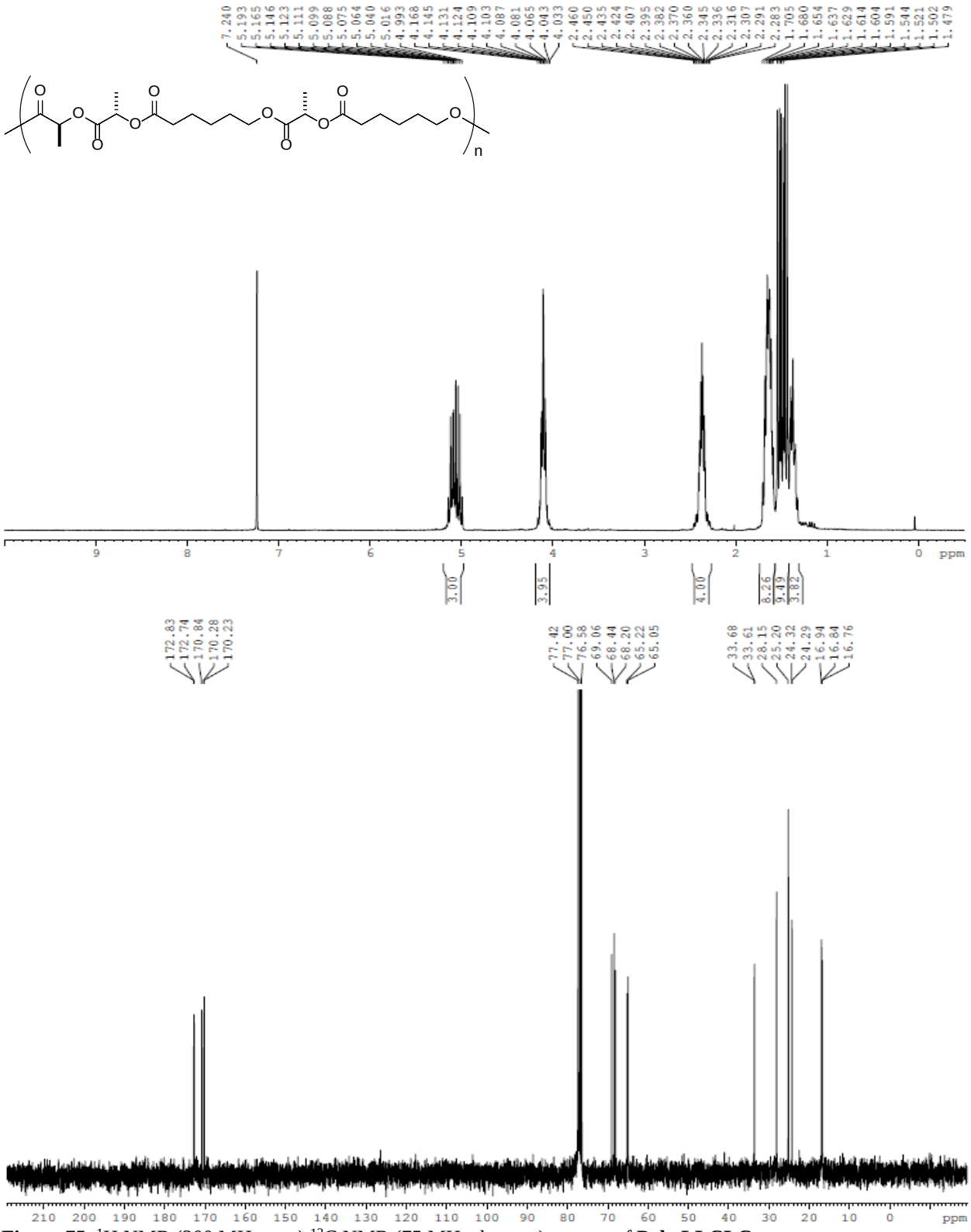


Figure 75. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LLCLC**.

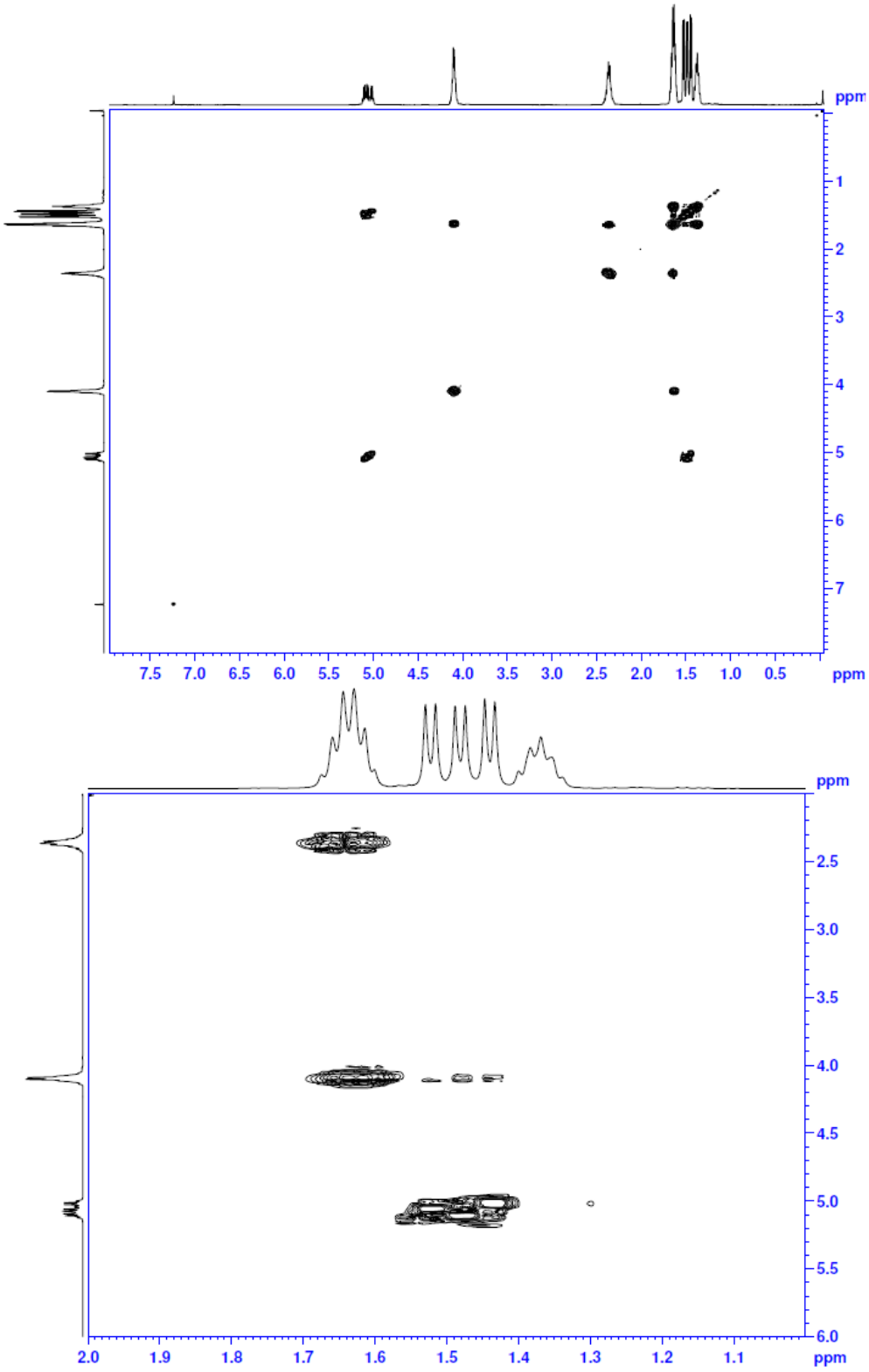


Figure 76. 2D HMBC NMR (500 MHz, top) spectrum and expansion (bottom) of **Poly LLCLC**.

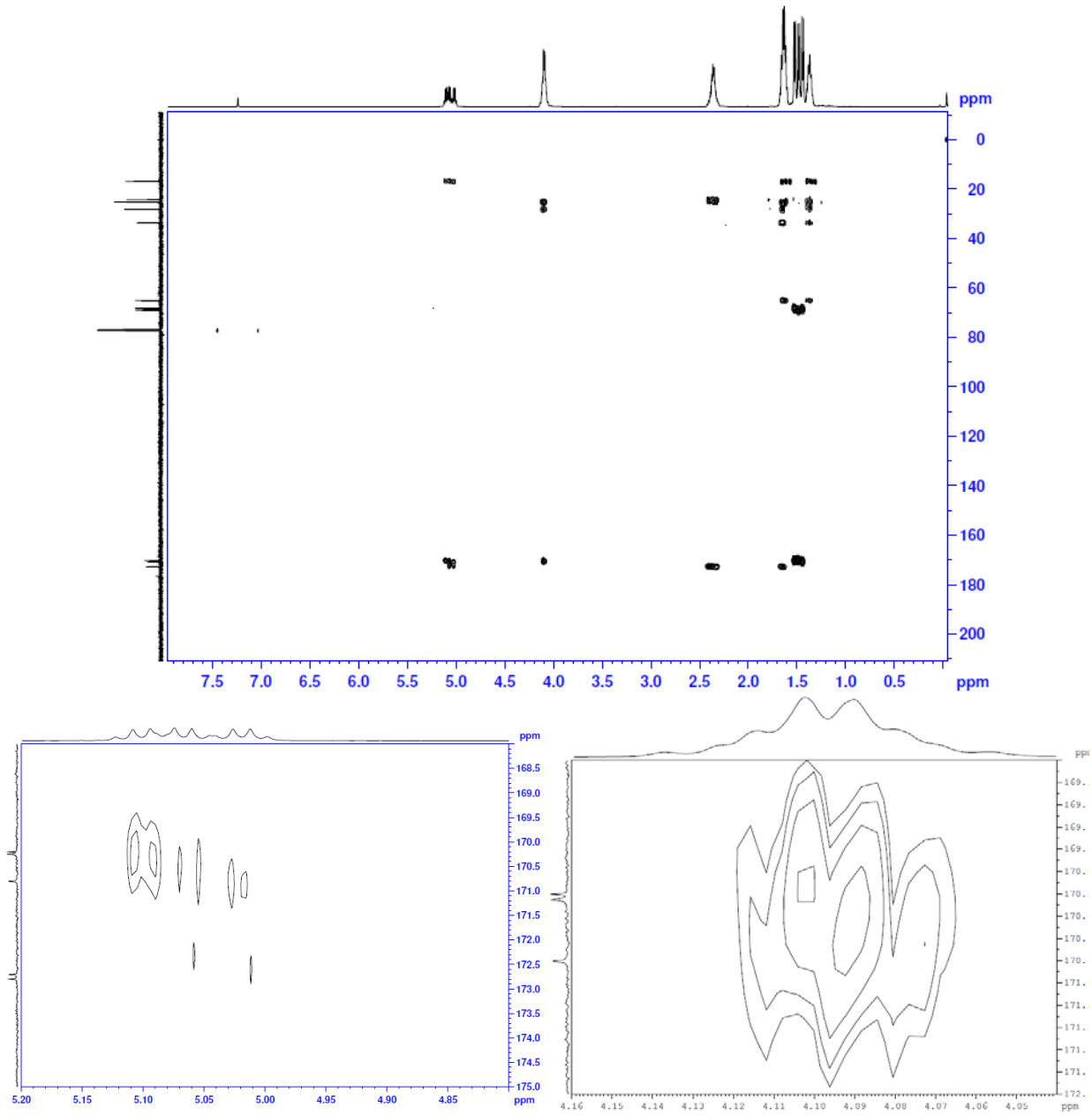


Figure 77. 2D HMBC NMR (500 – 125 MHz, top) spectrum and expansions (bottom left and right) of **Poly LLCLC**.

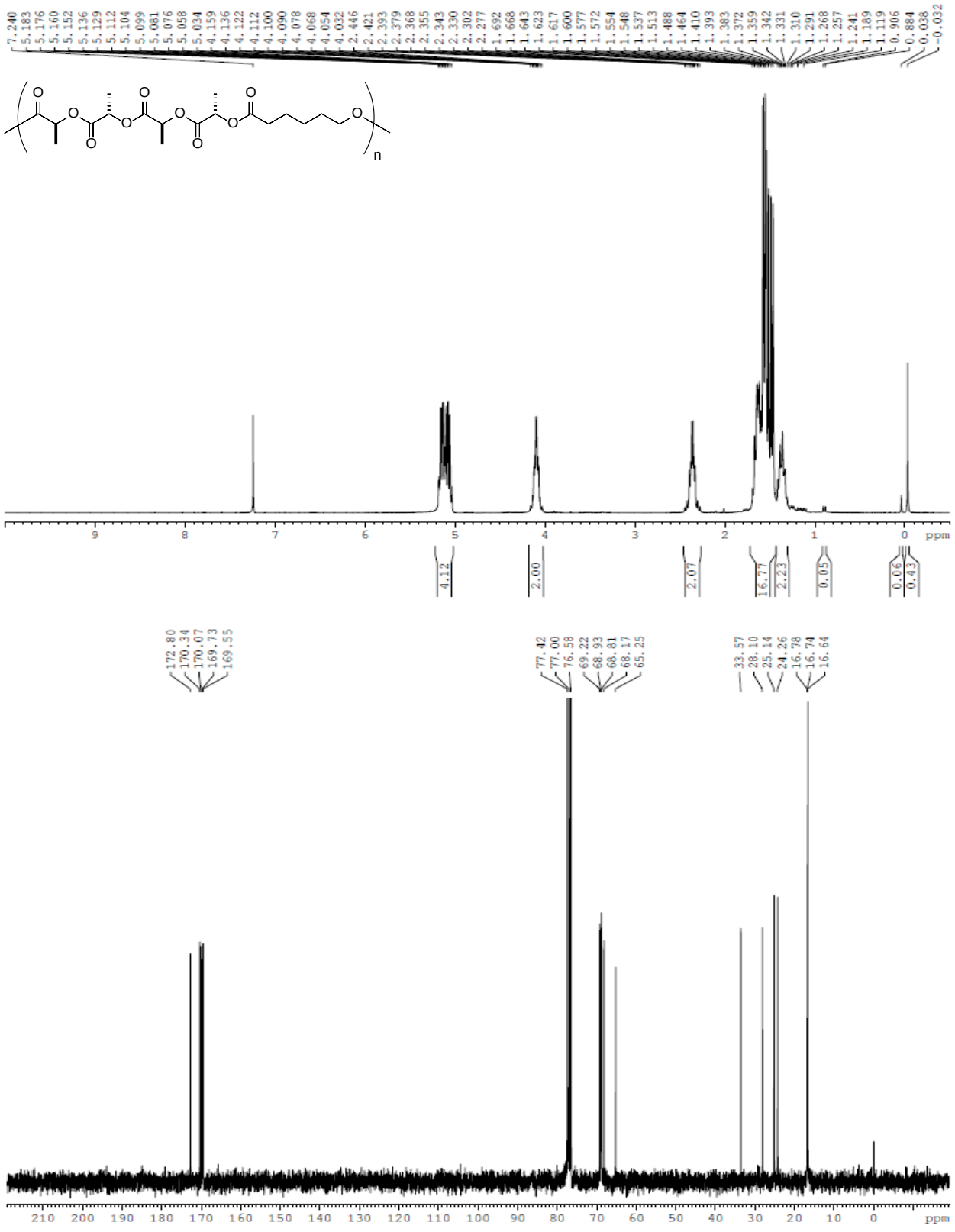


Figure 78. ^{1}H NMR (300 MHz, top) ^{13}C NMR (75 MHz, bottom) spectra of **Poly LLCLC**.

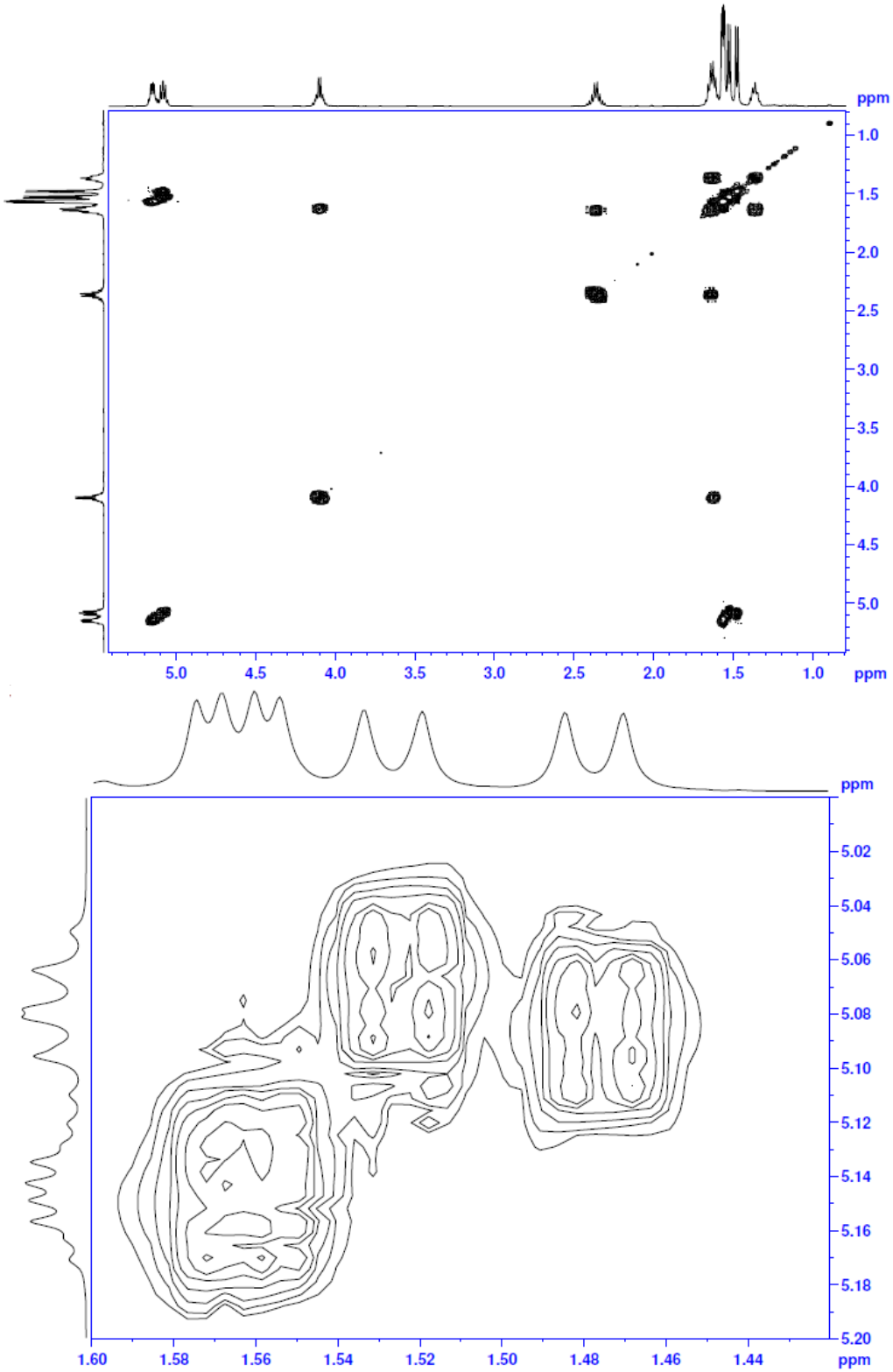


Figure 79. 2D COSY NMR (500 MHz, top) spectrum and expansion (bottom) of **Poly LLLLC**.

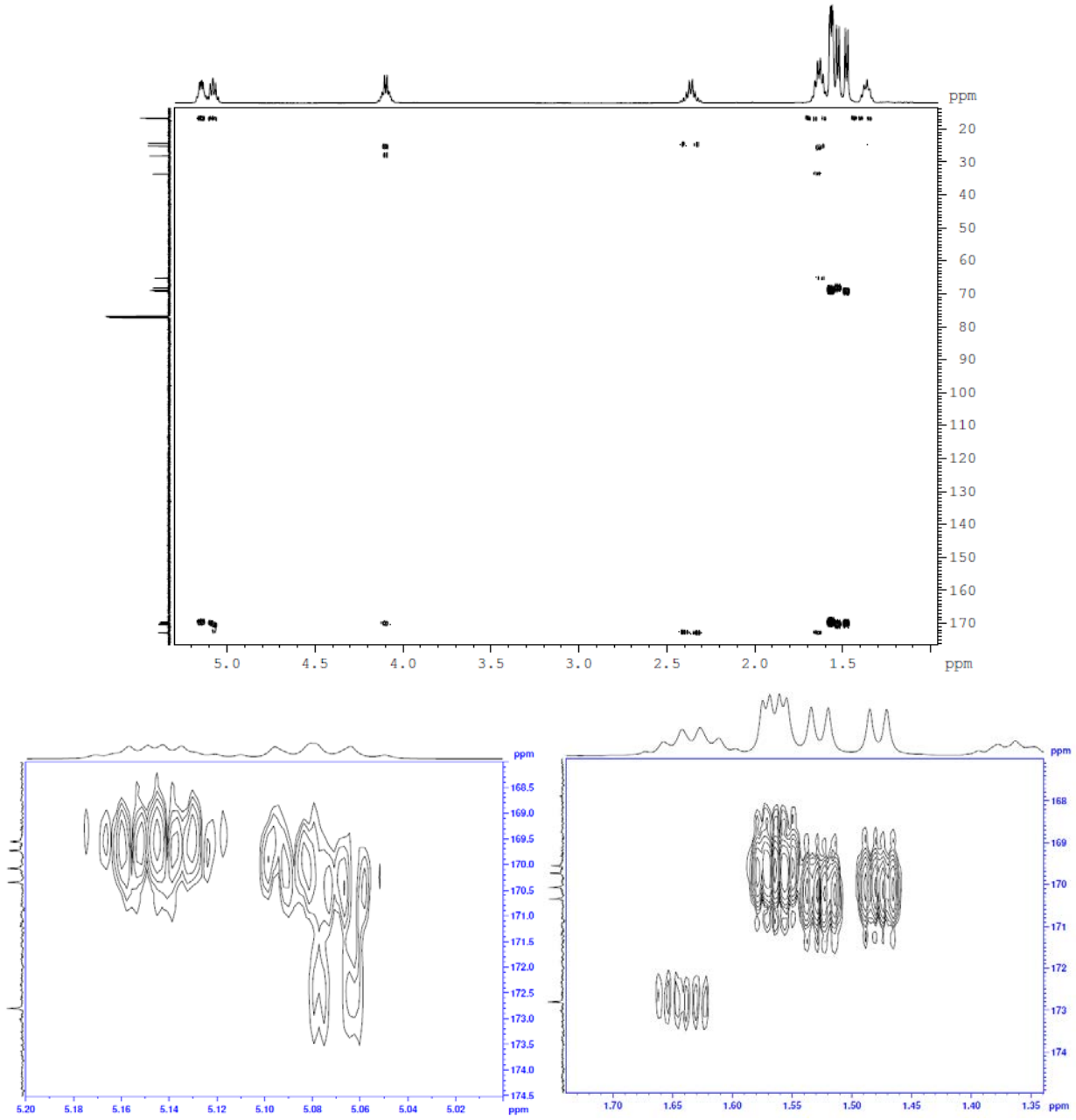


Figure 80. 2D COSY NMR (500 – 125 MHz, top) spectrum and expansion (bottom left and right) of **Poly LLLLC**.

A.2 DETERMINING SEQUENCE FIDELITY IN REPEATING SEQUENCE POLY(LACTIC-CO-GLYCOLIC ACIDS)

A.2.1 Data from maldi

Table 15. Intensity and percent error data determined by MALDI-TOF-MS of 1.7% errormer

Chain length (X)	(X+0L)X	(X+1L)*(X-1)	Correct	Total	SF (%)	ER (%)
6	13350	1600	14950	15270	97.90	2.10
7	16380	2526	18906	19327	97.82	2.18
8	22352	4984	27336	28048	97.46	2.54
9	26514	4816	31330	31932	98.11	1.89
10	38720	6939	45659	46430	98.34	1.66
11	53031	6970	60001	60698	98.85	1.15
12	63936	11165	75101	76116	98.67	1.33
13	77259	14664	91923	93145	98.69	1.31
14	92750	18161	110911	112308	98.76	1.24
15	99630	18718	118348	119685	98.88	1.12
16	82752	17925	100677	101872	98.83	1.17
17	59041	15904	74945	75939	98.69	1.31
18	44334	12631	56965	57708	98.71	1.29

Table 16. Intensity and percent error data determined by MALDI-TOF-MS of 2.4% errormer

Chain length (X)	(X+0L)X	(X+1L)*(X-1)	Correct	Total	SF (%)	ER (%)
8	149839	45761	195600	202137	96.8	3.2
9	135719	48368	184088	190134	96.8	3.2
10	146160	55366	201526	207678	97.0	3.0
11	180520	67128	247648	254361	97.4	2.6
12	164930	54761	219691	224669	97.8	2.2
13	162816	75189	238005	244271	97.4	2.6
14	150832	78625	229457	235505	97.4	2.6
15	153002	77287	230289	235810	97.7	2.3

Table 17. Intensity and percent error data determined by MALDI-TOF-MS of 5.0% errormer

Chain Length (X)	(X+0L)X	(X+1L)* (X-1)	(X+2L)* (X-2)	(X+3L)* (X-3)	Correct	Total	SF (%)	ER (%)
6	86070	17775	4792	1641	110278	117870	93.6	6.4
7	86730	28158	5890	2188	122966	131656	93.4	6.6
8	99616	36456	7140	1570	144782	153312	94.4	5.6
9	102366	40728	8834	2892	154820	163881	94.5	5.5
10	90830	44784	10136	3045	148795	157610	94.4	5.6
11	80707	44300	11718	3120	139845	148049	94.5	5.5
12	69528	40909	11140	3150	124727	131724	94.7	5.3
13	58331	42288	12507	3990	117116	124111	94.4	5.6
14	52346	39351	13236	3762	108695	114954	94.6	5.4
15	42915	35154	11973	3600	93642	98895	94.7	5.3

Table 18. Intensity and percent error data determined by MALDI-TOF-MS of 8.4% errormer

Chain Length (X)	(X+0L)X	(X+1L)* (X-1)	(X+2L)* (X-2)	(X+3L)* (X-3)	(X+4L)* (X-4)	Correct	Total	SF (%)	ER (%)
6	39912	25530	6488	1374	0	73304	83028	88.3	11.7
7	44982	34332	10620	2800	0	92734	104804	88.5	11.5
8	43840	43183	15468	3520	0	106011	119448	88.8	11.2
9	44964	46592	18116	5016	0	114688	128196	89.5	10.5
10	37960	48285	22640	6454	2370	117709	133080	88.4	11.6
11	33957	46670	25200	7128	2275	115230	129470	89.0	11.0
12	30252	42251	23400	9270	3072	108245	121392	89.2	10.8
13	24960	39852	26554	11360	3546	106272	119405	89.0	11.0
14	20342	35633	26340	12320	4820	99455	111874	88.9	11.1
15	16080	32494	25701	11292	4741	90308	101130	89.3	10.7
16	13248	22080	21098	11700	4608	72734	81456	89.3	10.7

Table 19. Intensity and percent error data determined by MALDI-TOF-MS of 11.6% errormer

Chain Length (X)	(X+0L)X	(X+1L)* (X-1)	(X+2L)* (X-2)	(X+3L)* (X-3)	(X+4L)* (X-4)	Correct	Total	SF (%)	ER (%)
6	28422	24475	8712	2340	---	63949	75540	84.7	15.3
7	29729	33276	12820	4012	---	79837	93520	85.4	14.6
8	27888	40600	18660	5165	---	92313	107432	85.9	14.1
9	27072	41144	22036	7350	---	97602	112716	86.6	13.4
10	22820	40536	25272	8925	3234	100787	117590	85.7	14.3
11	17523	36760	25452	10184	3507	93426	108581	86.0	14.0
12	14988	32670	23440	12438	4312	87848	101808	86.3	13.7
13	11817	26640	25960	12860	4995	82272	95290	86.3	13.7
14	10430	22165	22740	12430	5360	73125	84154	86.9	13.1
15	8340	17192	19214	12996	5940	63682	73275	86.9	13.1
16	6608	14580	17696	10920	5784	55588	63536	87.5	12.5
17	4301	10496	13440	12236	6045	46518	53448	87.0	13.0
18	3888	8755	11280	9150	5558	38631	43974	87.8	12.2
19	3325	6750	8687	8656	5655	33073	37601	88.0	12.0
20	2500	5586	7290	7344	5520	28240	32020	88.2	11.8
21	1701	3740	6612	4662	3927	20642	23226	88.9	11.1

A.2.2 ^{1}H NMR spectra and data of Poly LG “errormers”

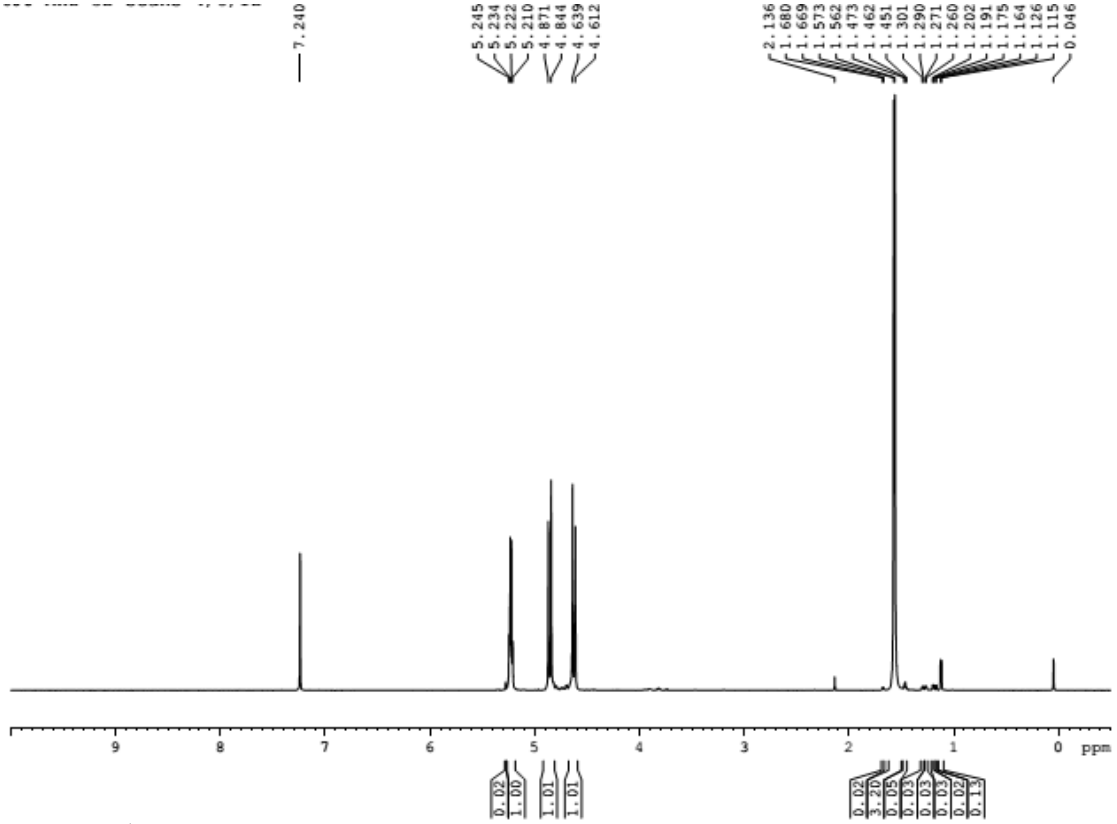


Figure 81. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 0% errormer.

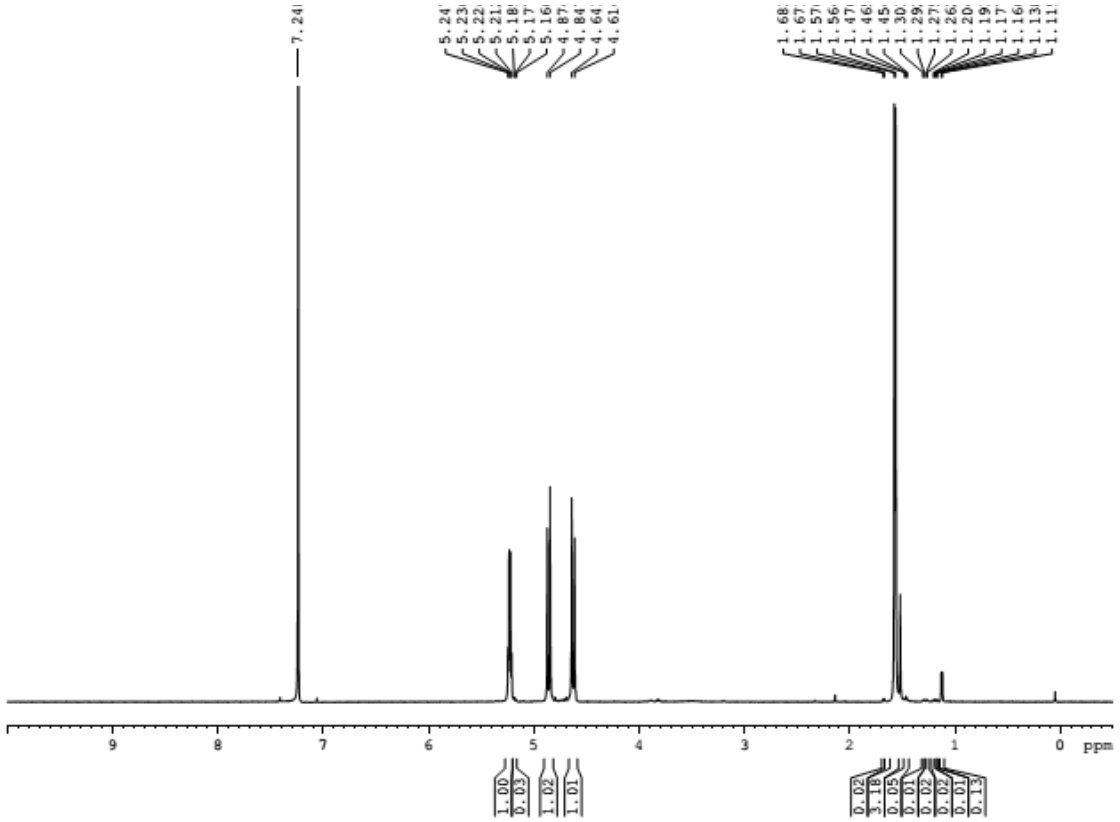


Figure 82. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 1.7% errormer.

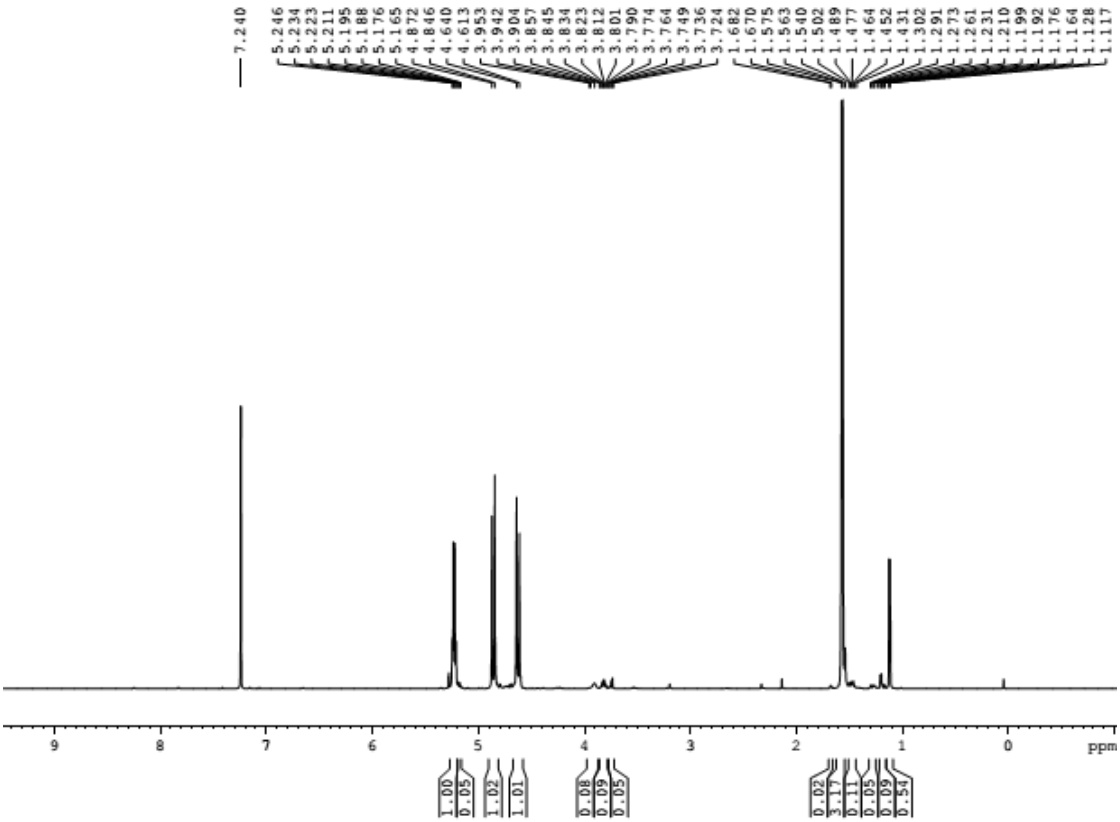


Figure 83. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 2.4% errormer.

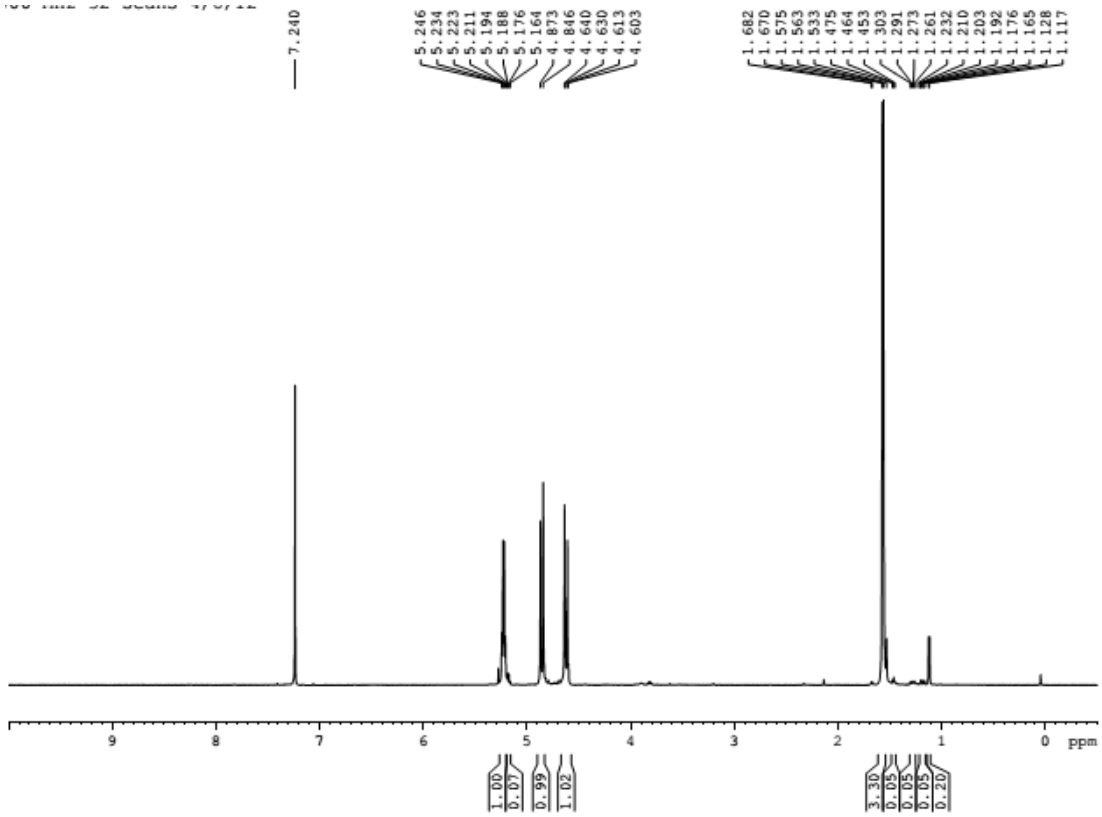


Figure 84. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 5.0% errormer.

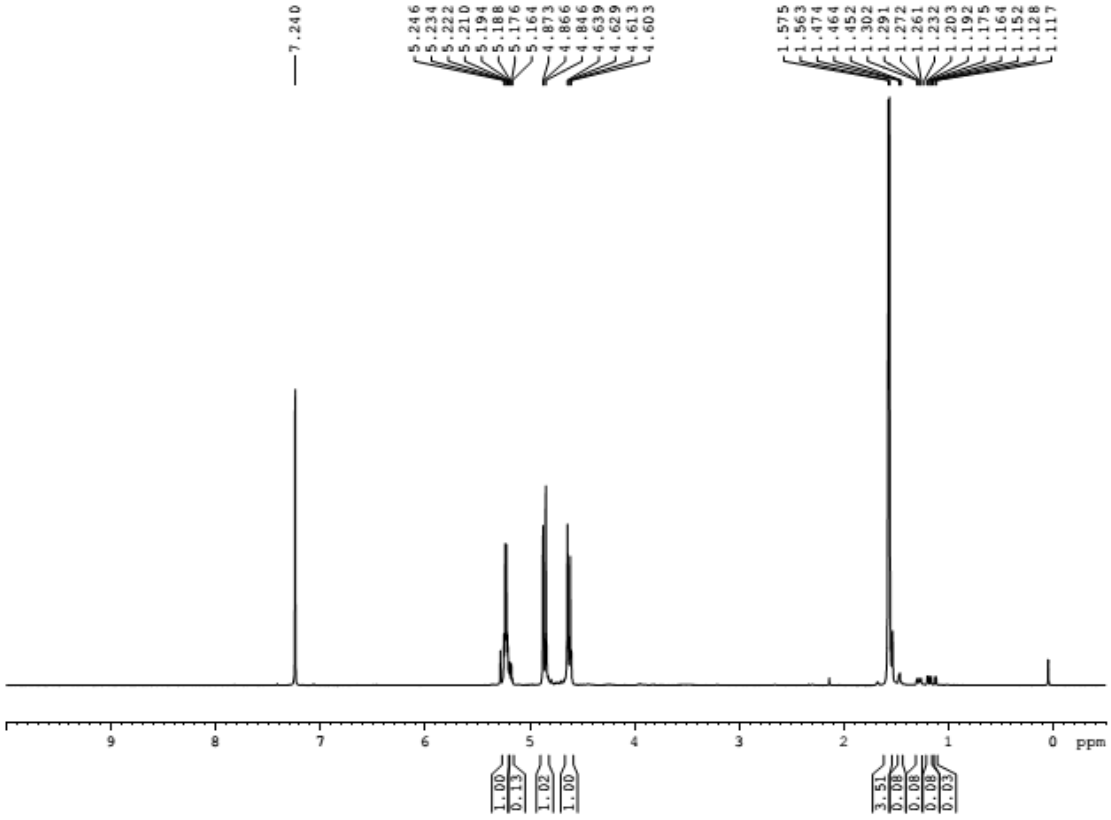


Figure 85. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 8.4% errormer.

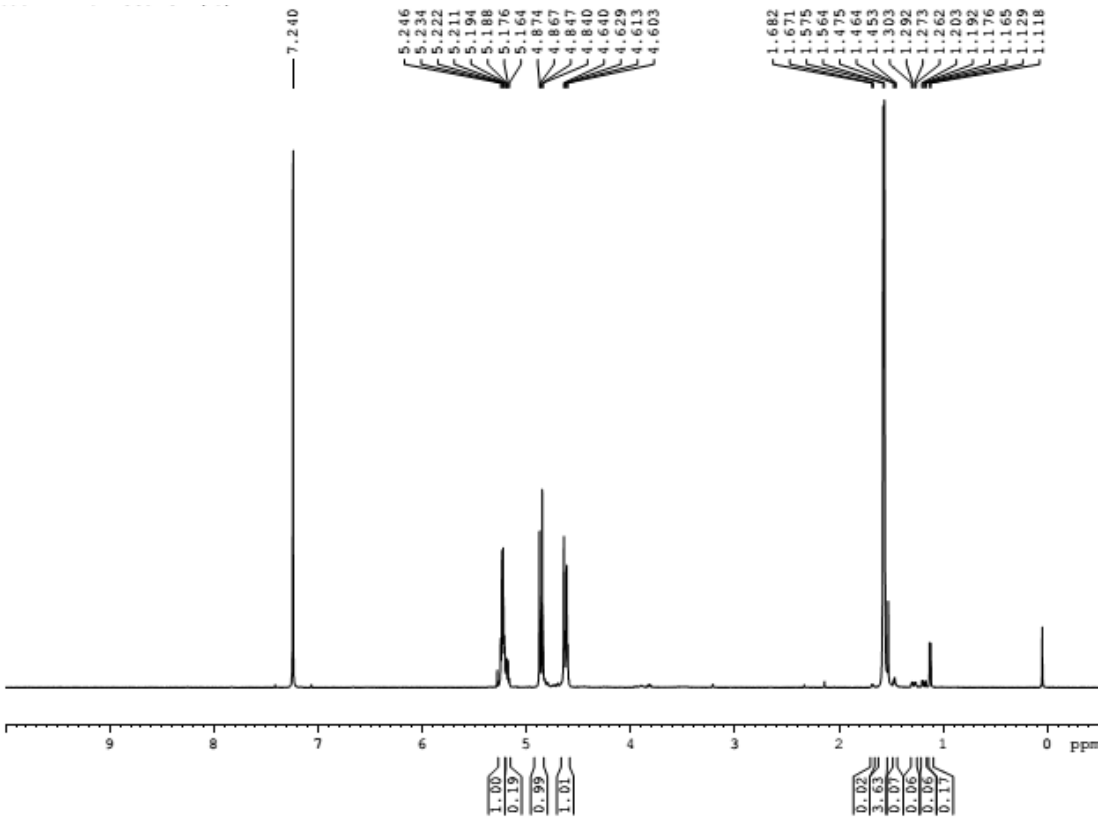


Figure 86. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of poly LG 11.6% errormer.

Table 20. ^{1}H NMR integration data of Poly LG errormers

Polymer	Each part of 1/2 quartet integrated		1/2 quartet	1 quartet (A)	2 quartet	Total Integration from NMR	Total Int - 2 L error quart (B)	A/(2A+B)	Percent error
1.7% errormer	0.0086	0.0032	0.012	0.024	0.047	1.03	0.99	0.023	2.3
2.4% errormer	0.014	0.0079	0.022	0.043	0.086	1.04	0.96	0.041	4.1
5.0% errormer	0.021	0.0080	0.029	0.059	0.12	1.09	0.98	0.054	5.4
8.4% errormer	0.050	0.016	0.066	0.13	0.26	1.16	0.90	0.113	11.3
11.6% errormer	0.059	0.020	0.079	0.16	0.32	1.19	0.87	0.133	13.3

A.2.3 MALDI-ToF spectra of Poly LG “errormers”

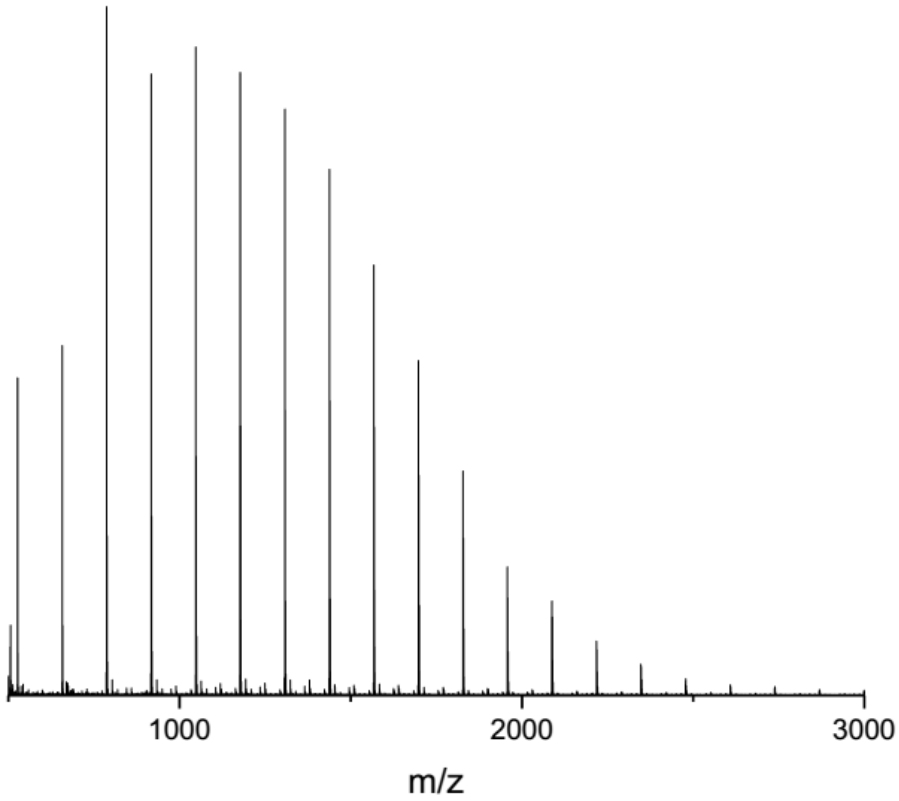


Figure 87. MALDI-ToF spectrum of Poly LG “errormer” 0% L error (0%-errormer)

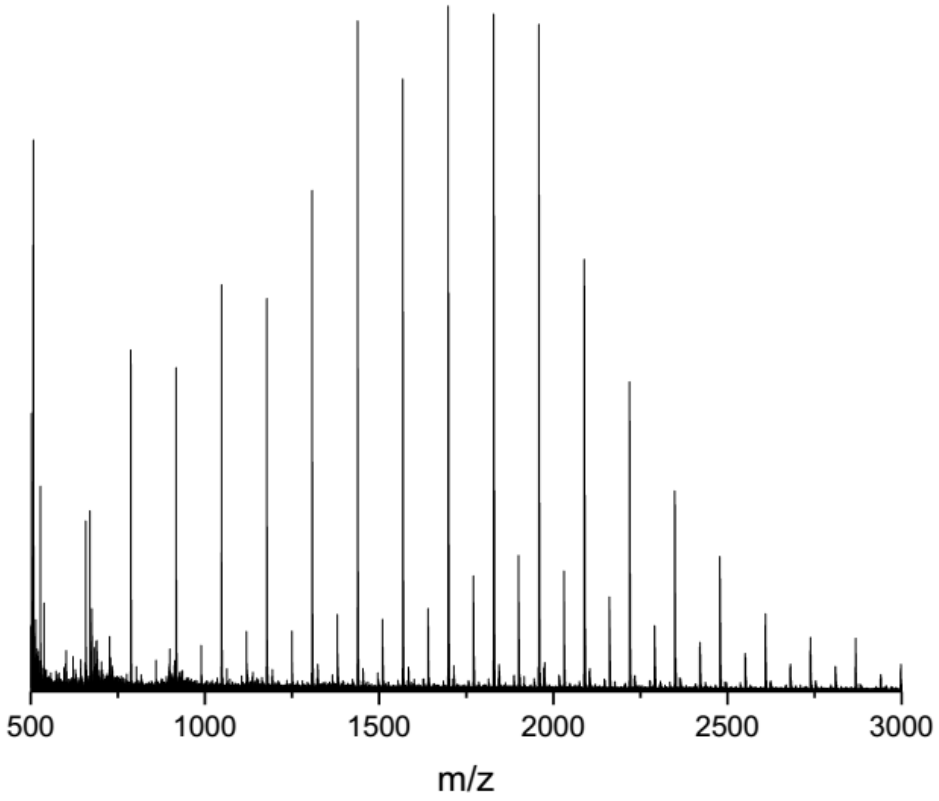


Figure 88. MALDI-ToF spectrum of Poly LG “errormer” 1.7% L error (1.7%-errormer)

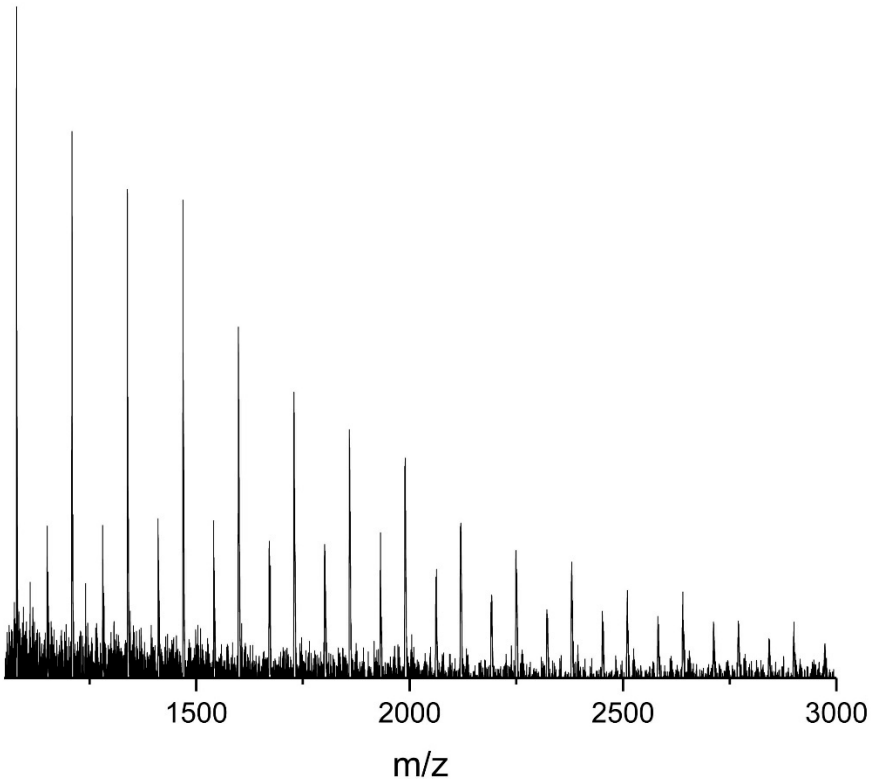


Figure 89. Low-resolution MALDI-ToF spectrum of Poly LG “errormer” 2.4% L error (2.4%-errormer)

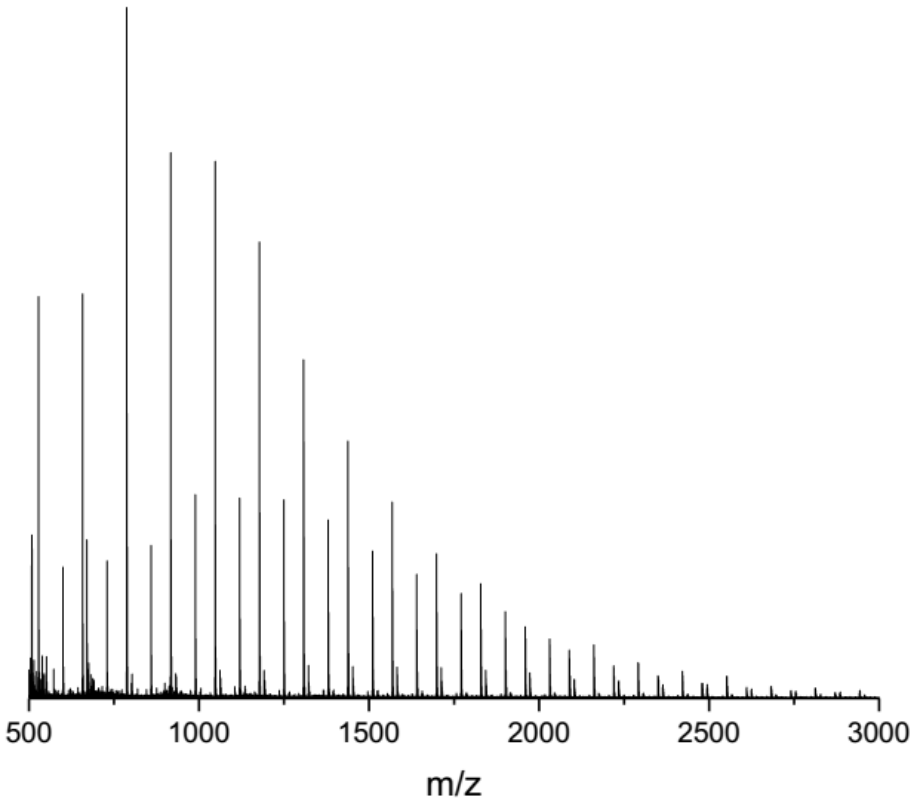


Figure 90. MALDI-ToF spectrum of Poly LG “errormer” 5.0% L error (5.0%-errormer)

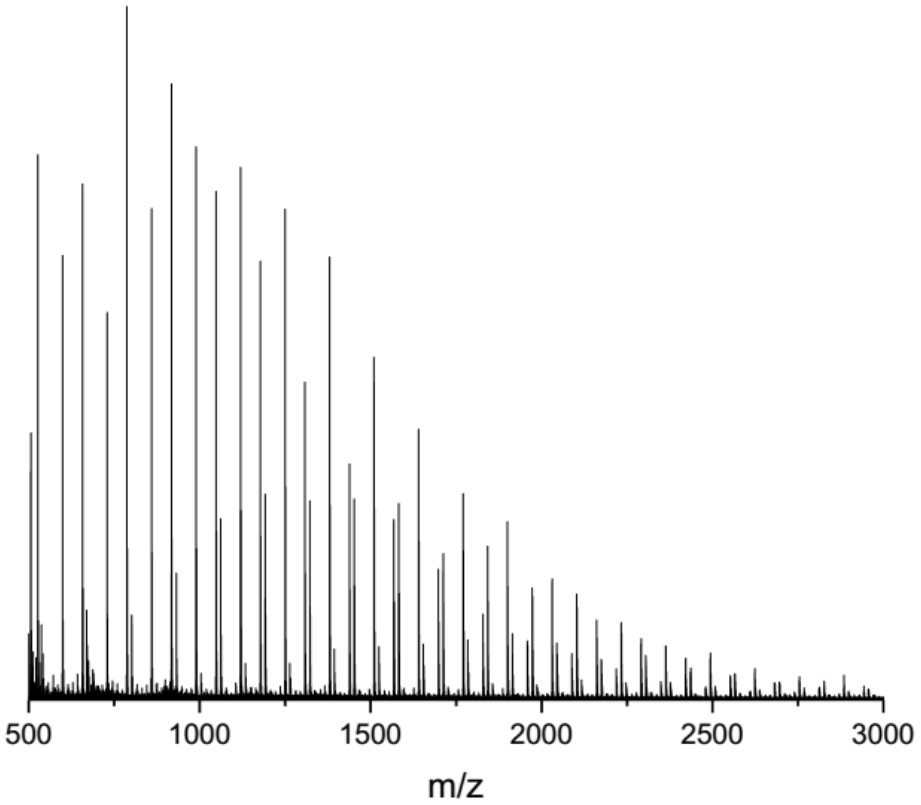


Figure 91. MALDI-ToF spectrum of Poly LG “errormer” 8.4% L error (8.4%-errormer)

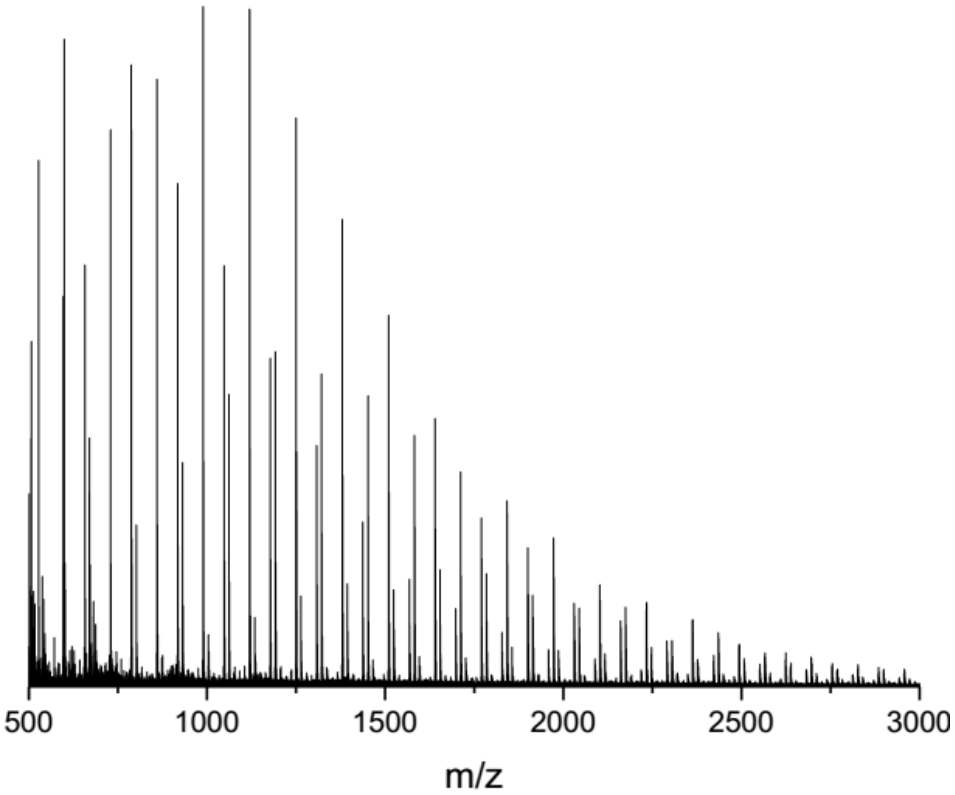


Figure 92. MALDI-ToF spectrum of Poly LG “errormer” 11.6% L error (11.6%-errormer)

A.3 SEQUENCE-CONTROLLED COPOLYMERS PREPARED VIA ENTROPY-DRIVEN RING-OPENING METATHESIS POLYMERIZATION

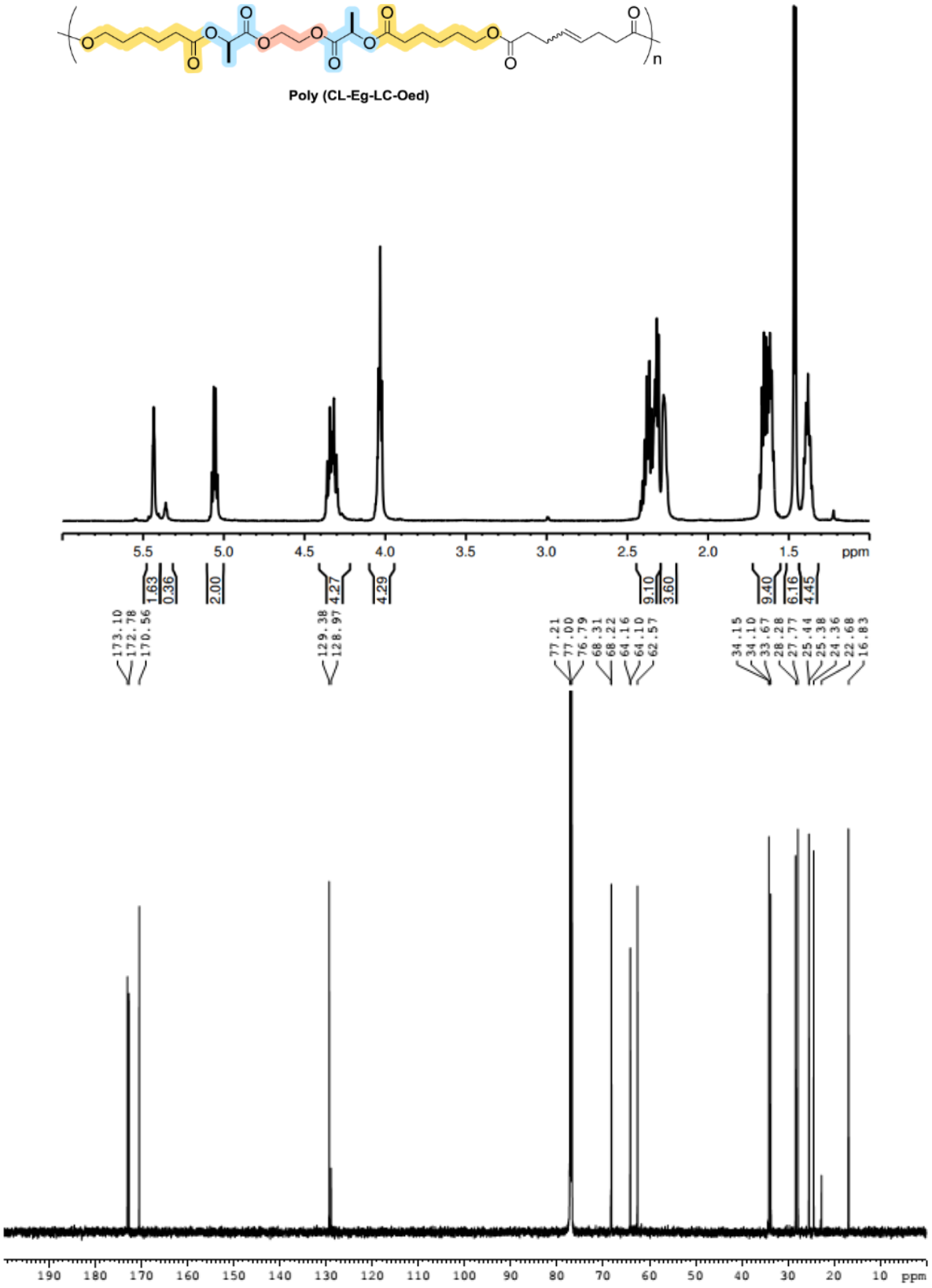


Figure 93. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (150 MHz, bottom) spectra of **poly (CL-Eg-LC-Oed)**.

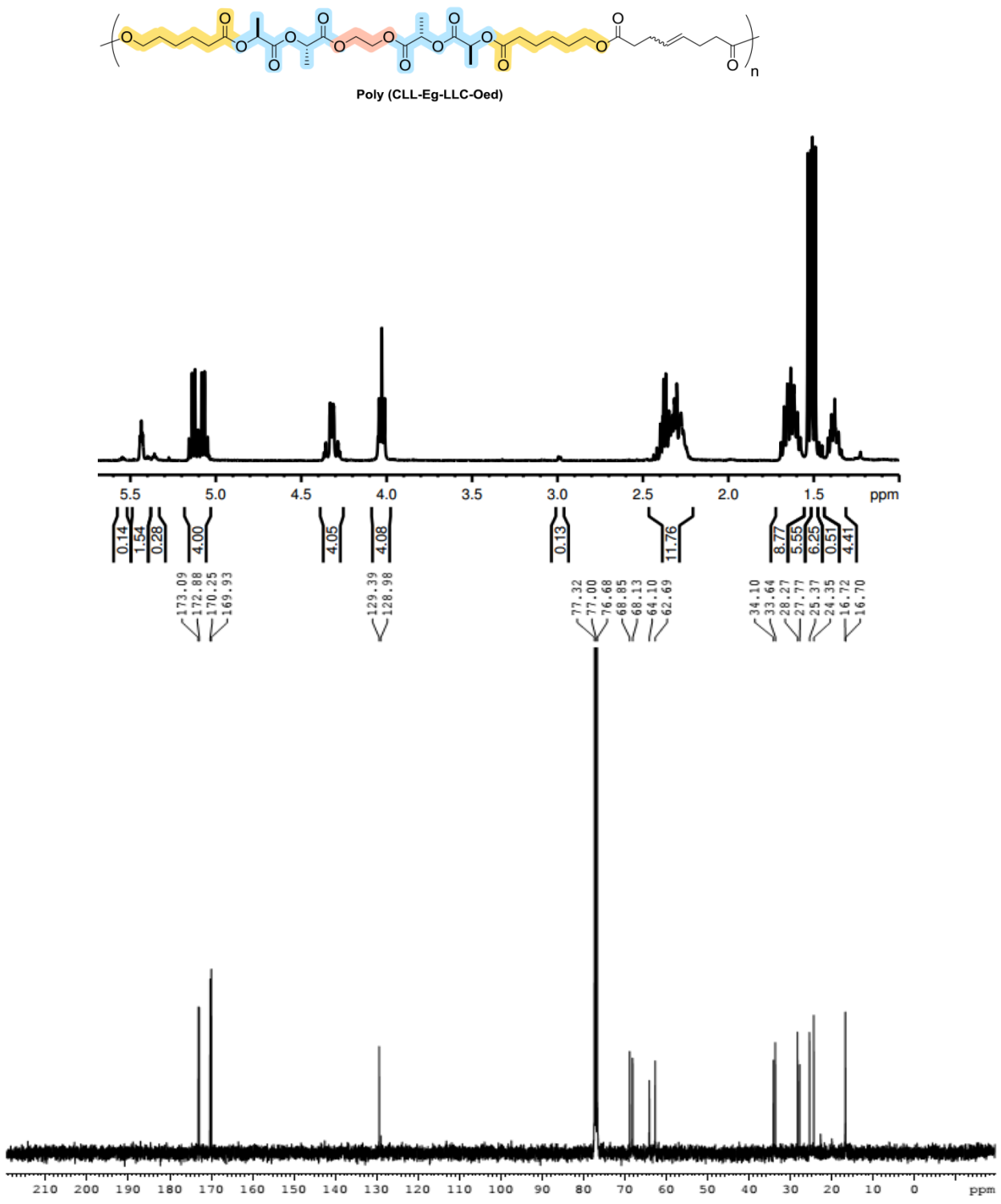


Figure 94. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz, bottom) spectraof **poly (CLL-Eg-LLC-Oed)-4**

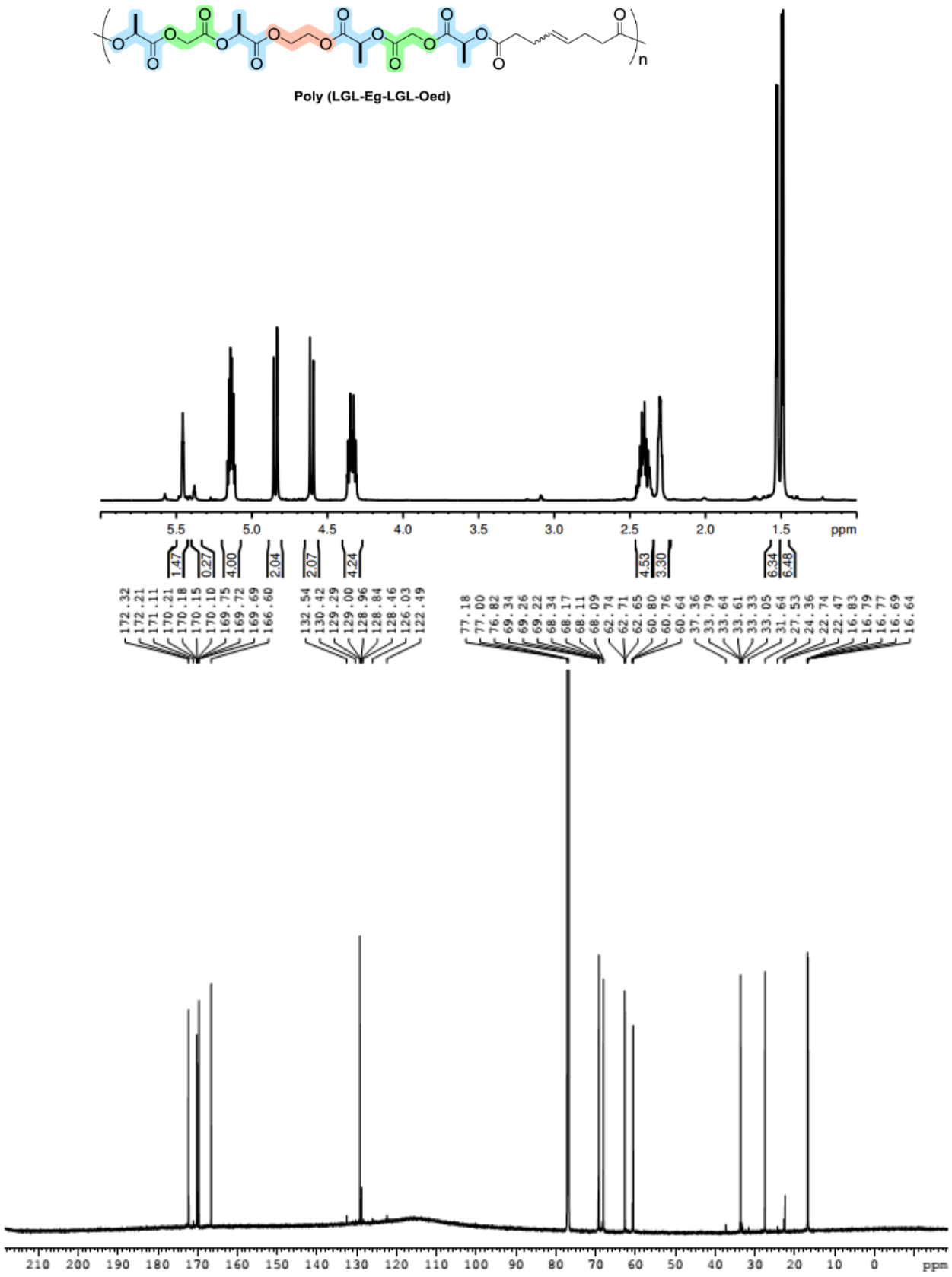


Figure 95. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra of **poly (LGL-Eg-LGL-Oed)**.

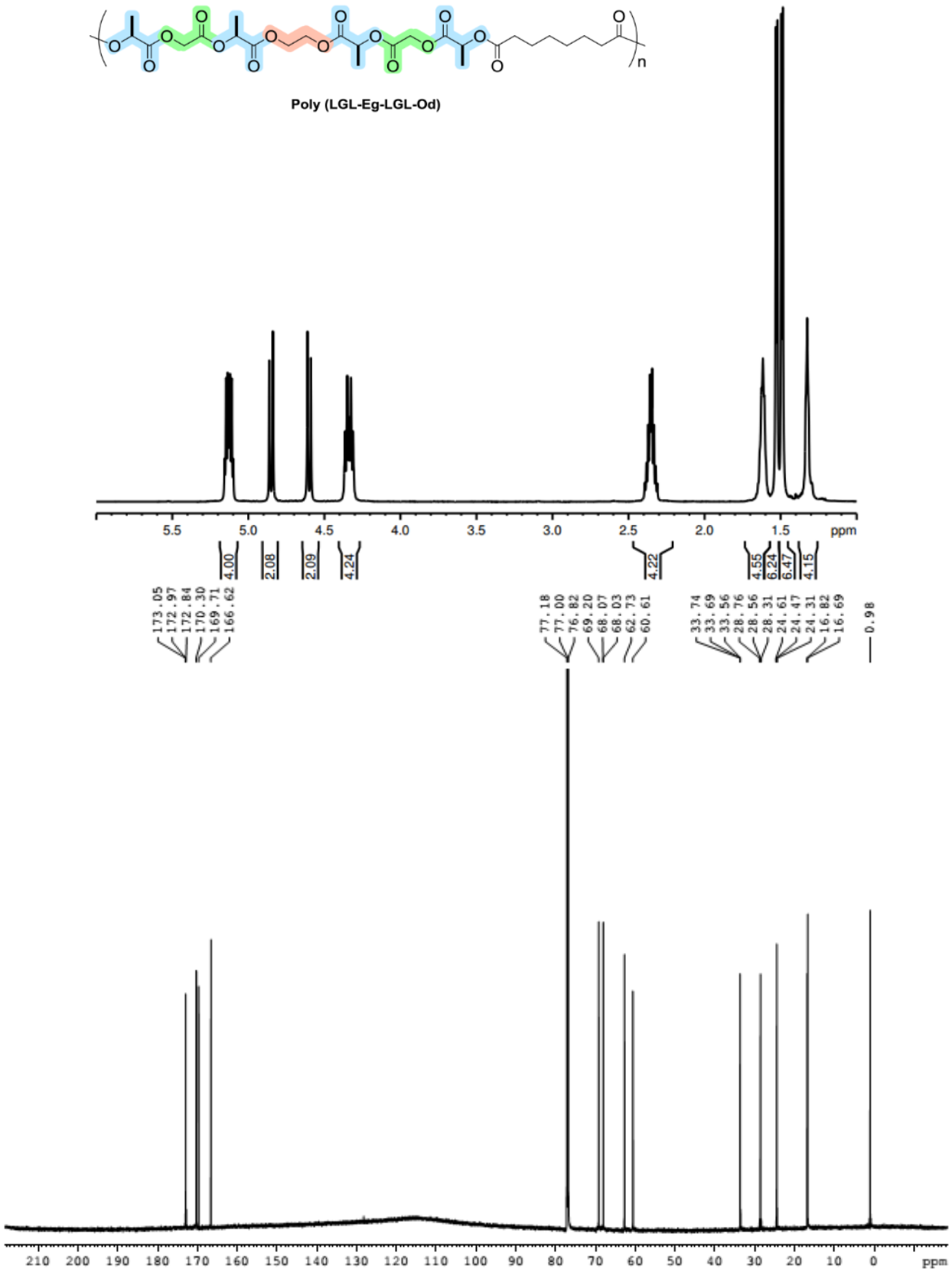


Figure 96. ^{1}H (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra of **poly (LGL-Eg-LGL-Od)**

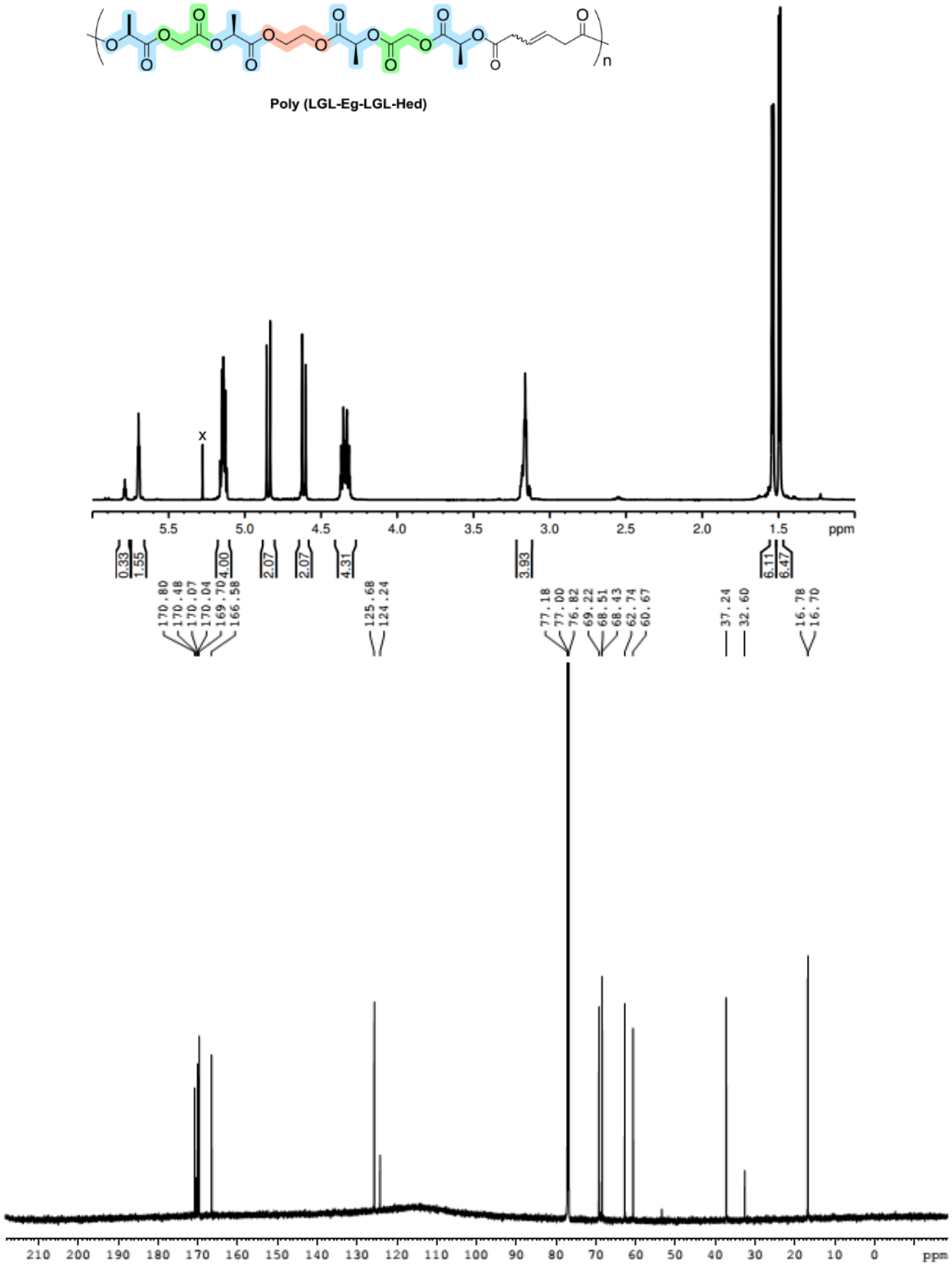


Figure 97. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra of **poly (LGL-Eg-LGL-Hed)**

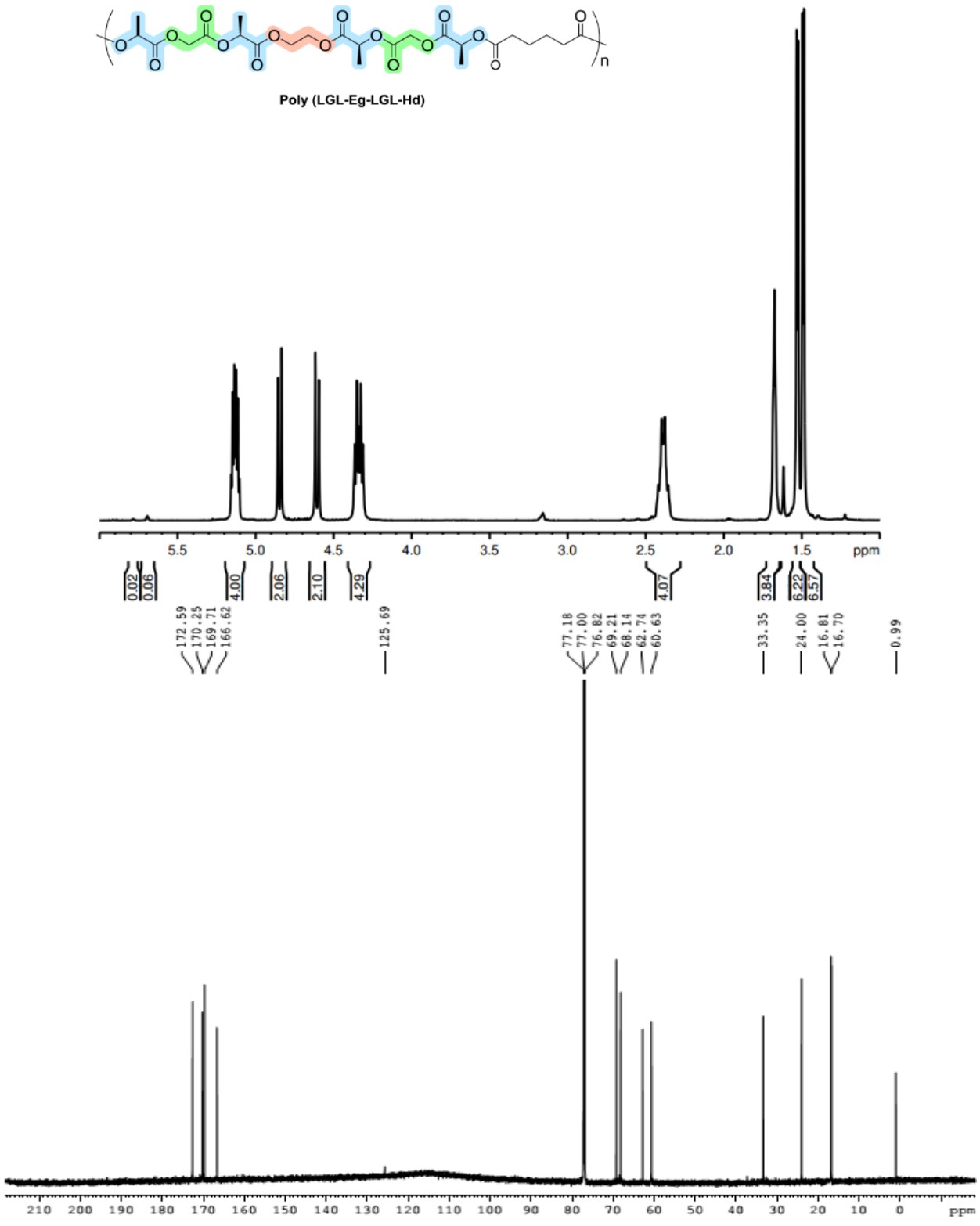


Figure 98. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra of **poly (LGL-Eg-LGL-Hd)**.

A.4 SYNTHESIS AND PREPARATION OF SEQUENCED PLGA STEREOCOMPLEXES

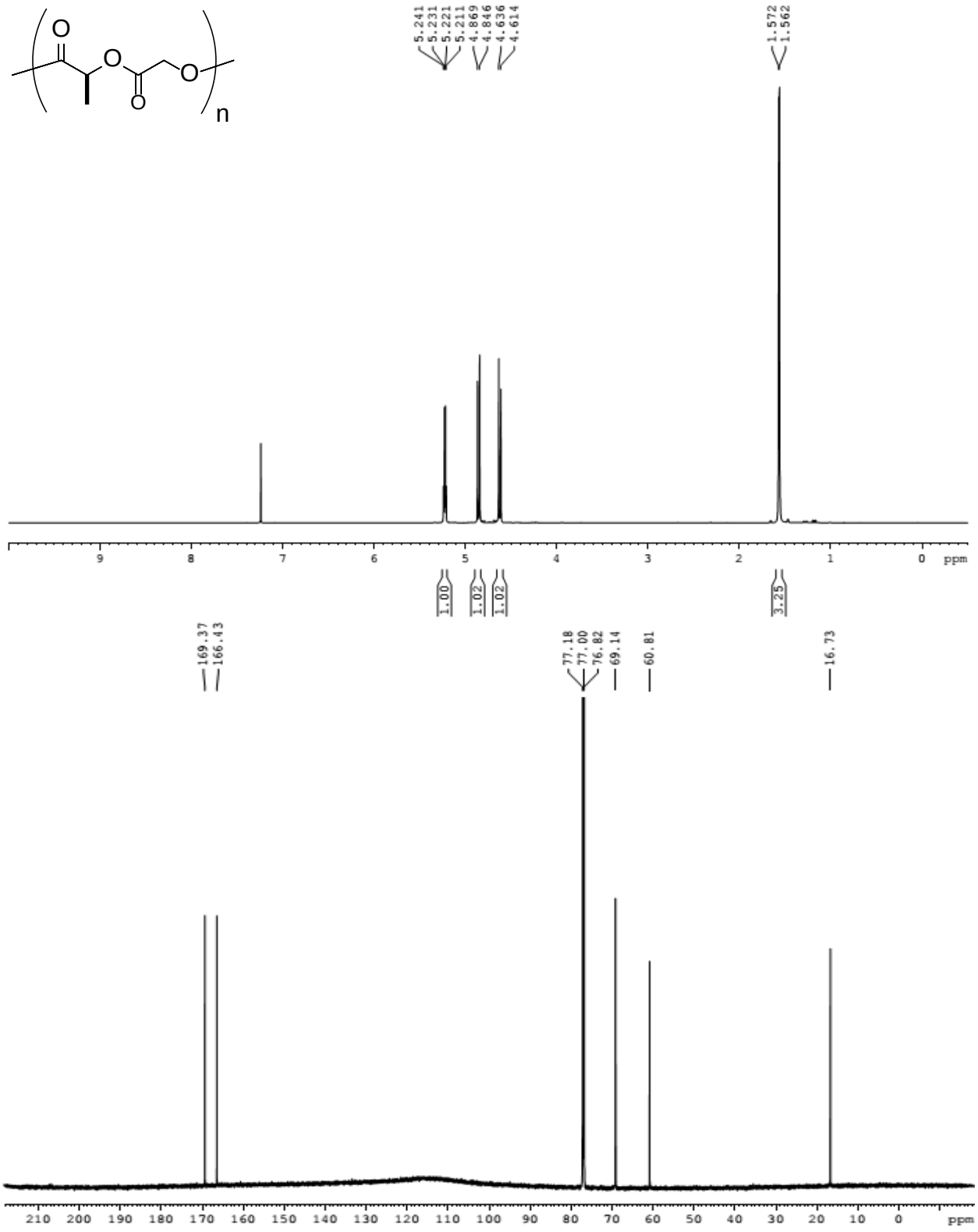


Figure 99. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly LG**.

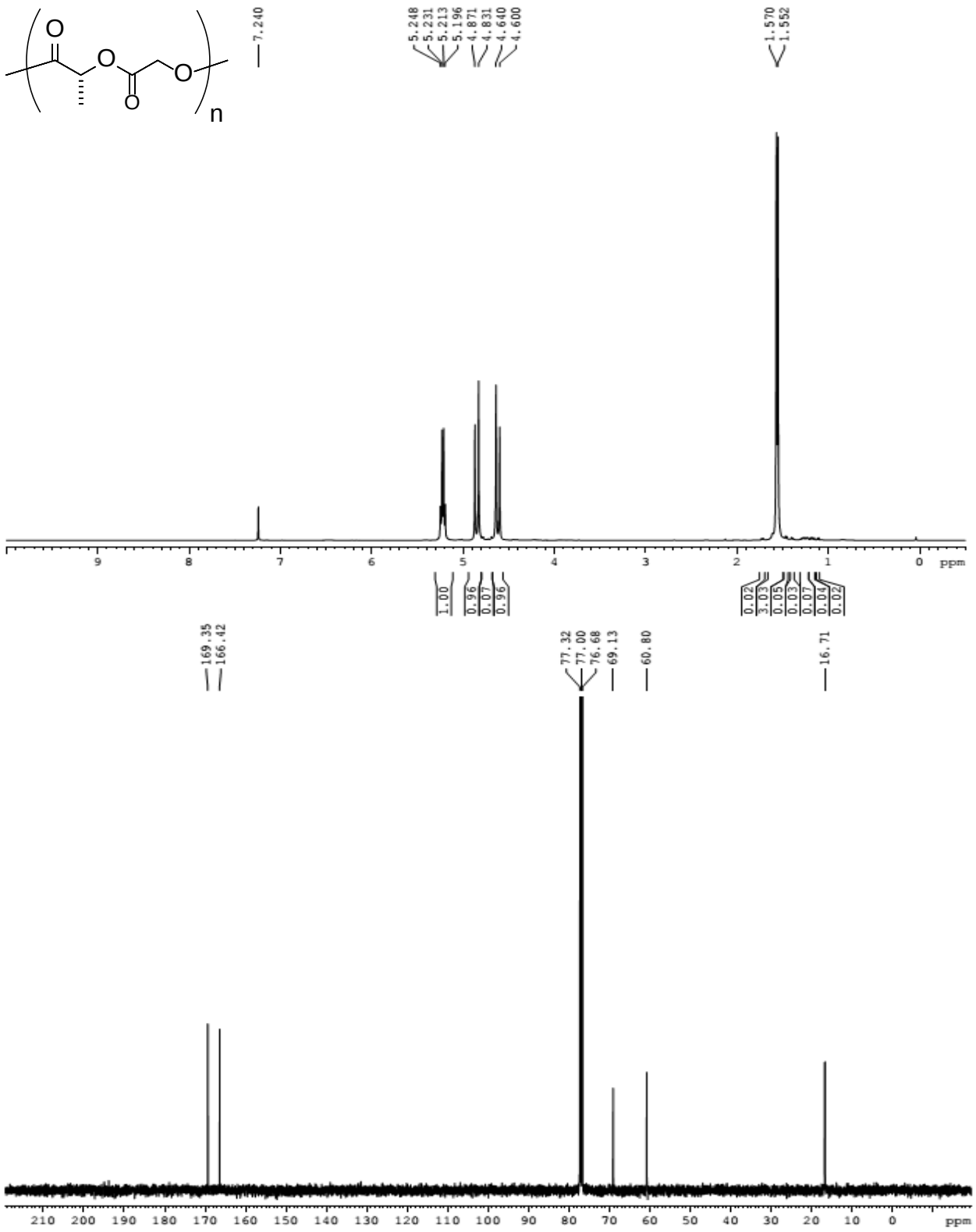


Figure 100. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly L$_R$G**.

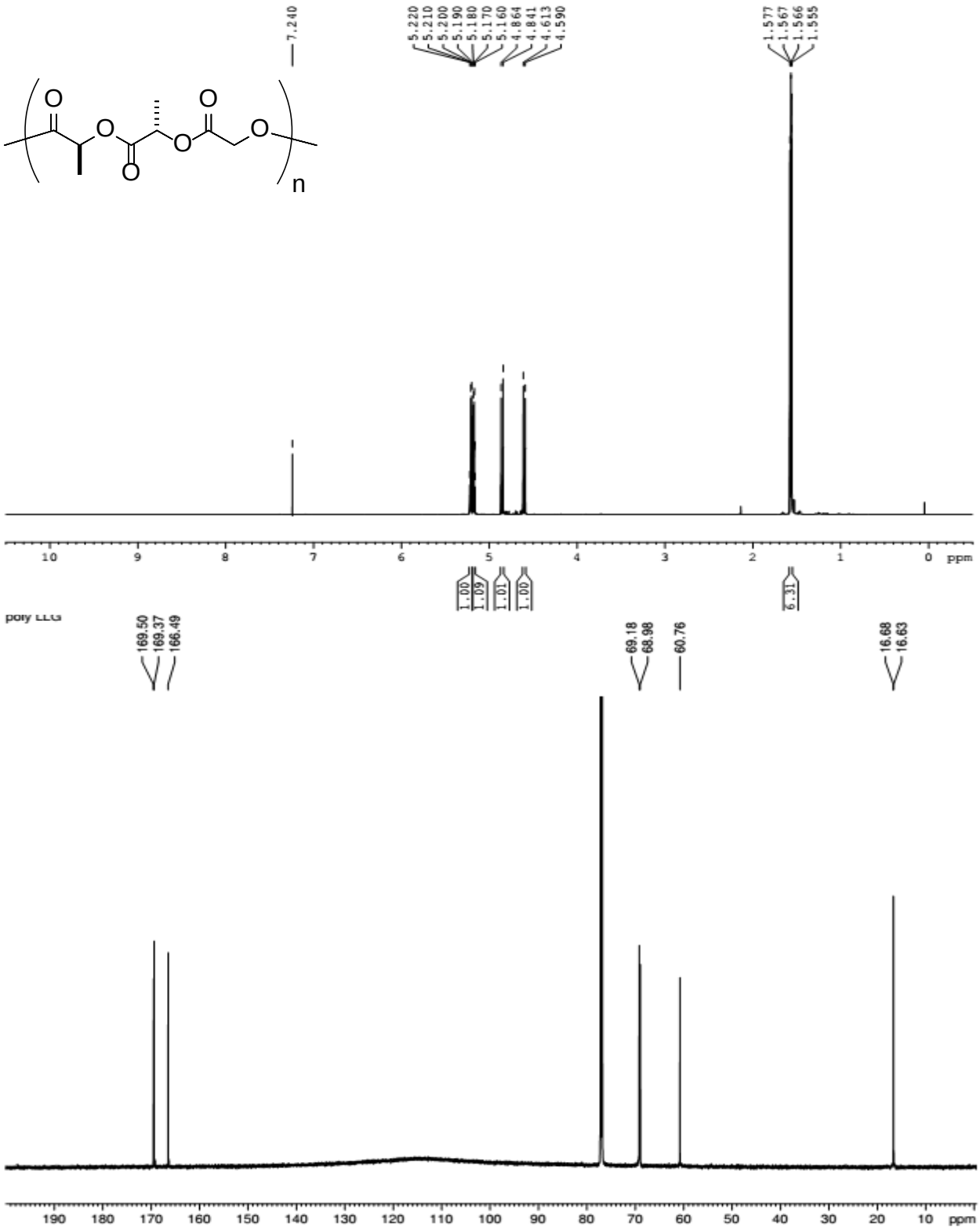


Figure 101. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly LLG**. These spectra were obtained from Stayshich *et al.*[15,176]

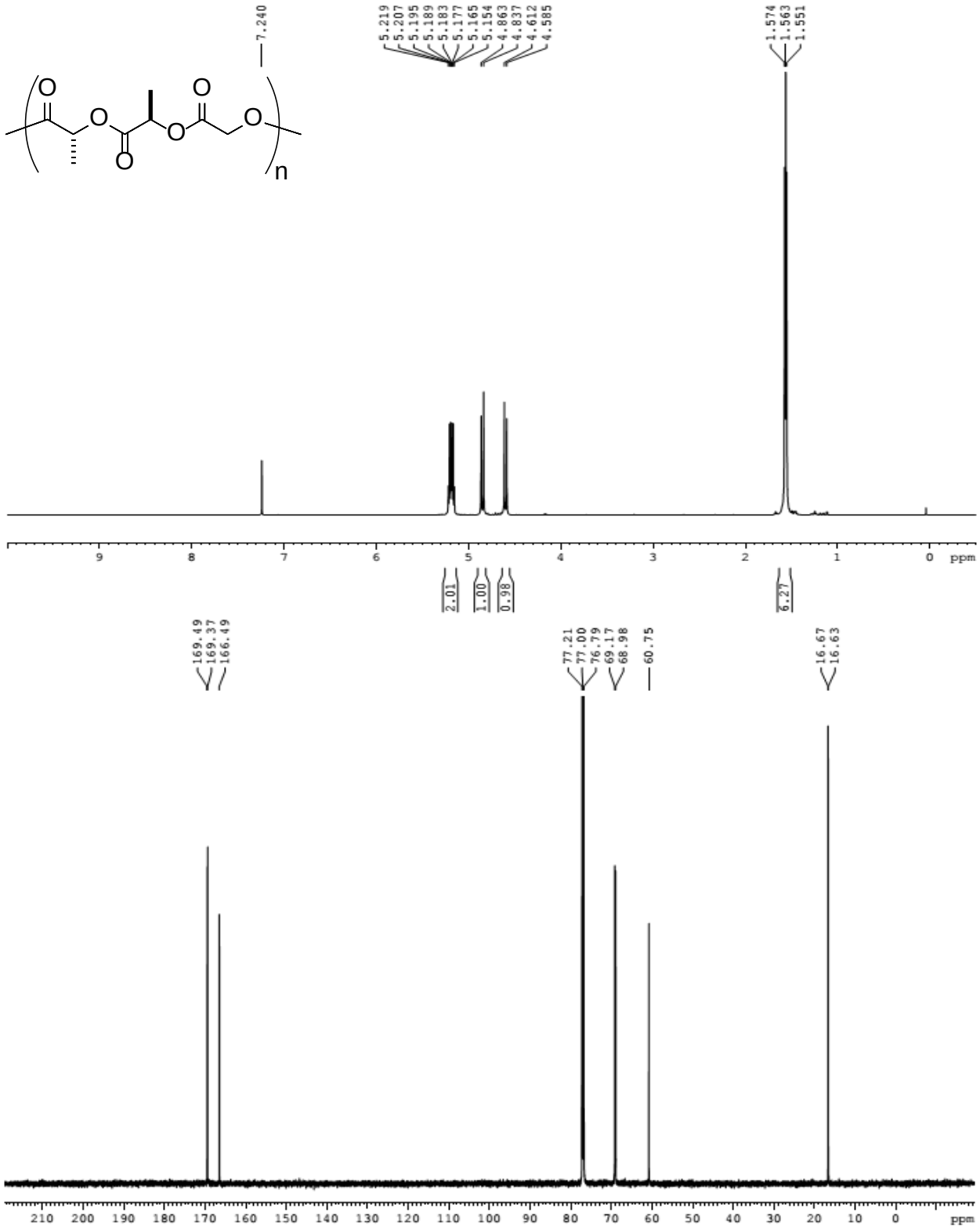


Figure 102. ^{1}H NMR (600 MHz, top) ^{13}C NMR (150 MHz, bottom) spectra of **Poly L$_R$L$_R$G**.

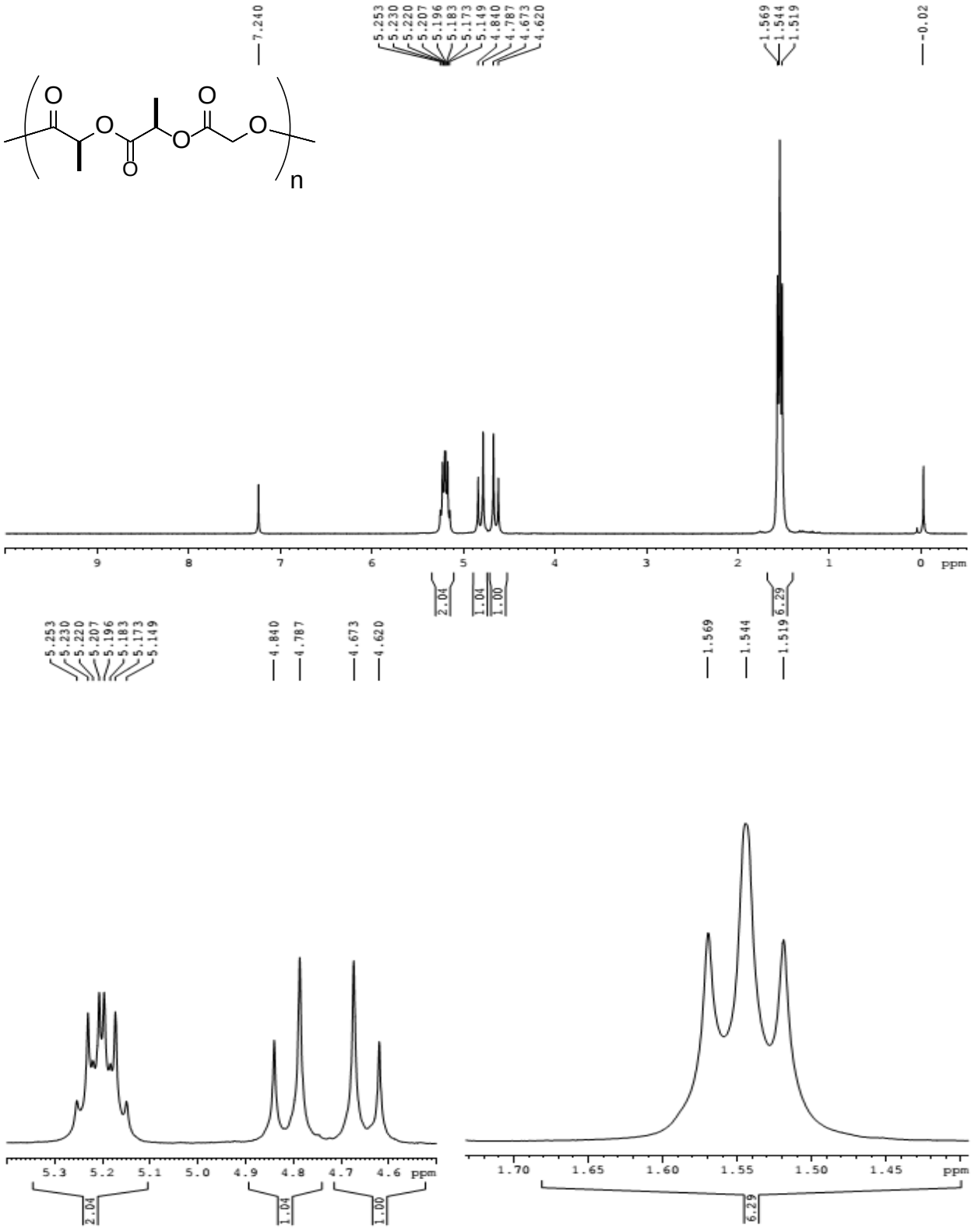


Figure 103. [1]H NMR (300 MHz, top) [1]H NMR (100 MHz, enhanced region bottom) spectra of **Poly LL$_R$G**. See Stayshich *et al.* for high resolution spectra.[15,162]

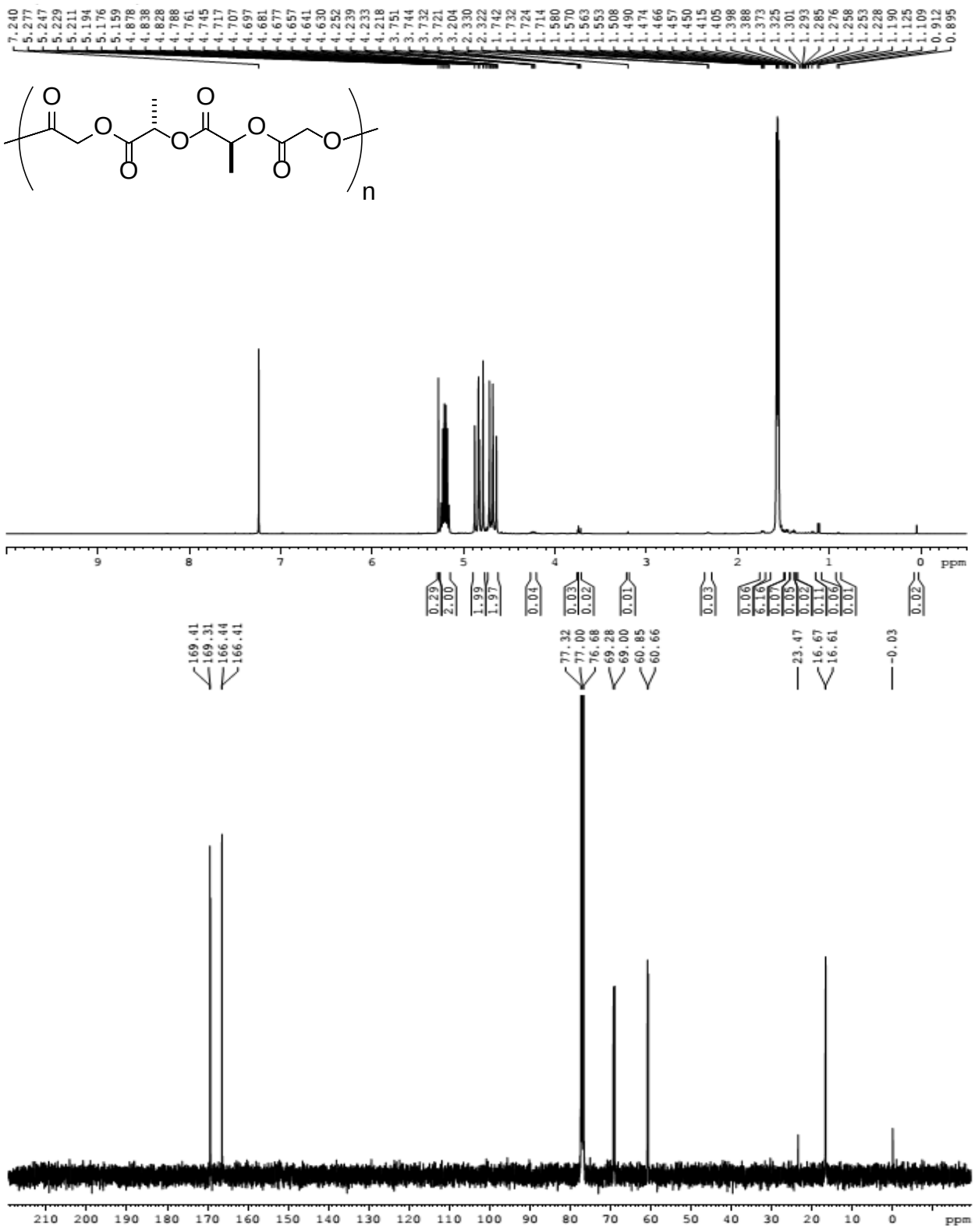


Figure 104. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly GLLG**. Prepared by Michael Washington.

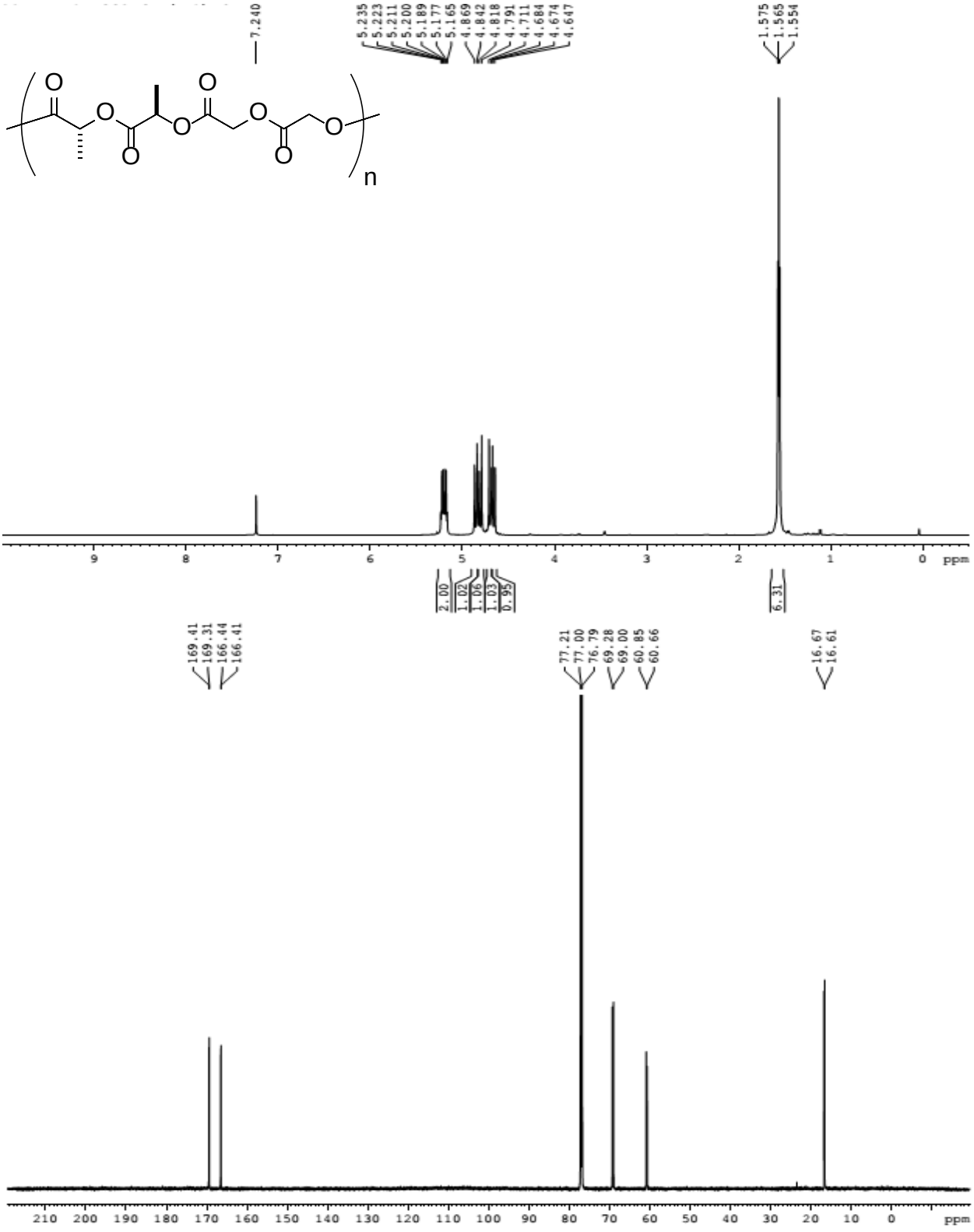


Figure 105. ^{1}H NMR (600 MHz, top) ^{13}C NMR (150 MHz, bottom) spectra of **Poly L$_R$L$_R$GG**.

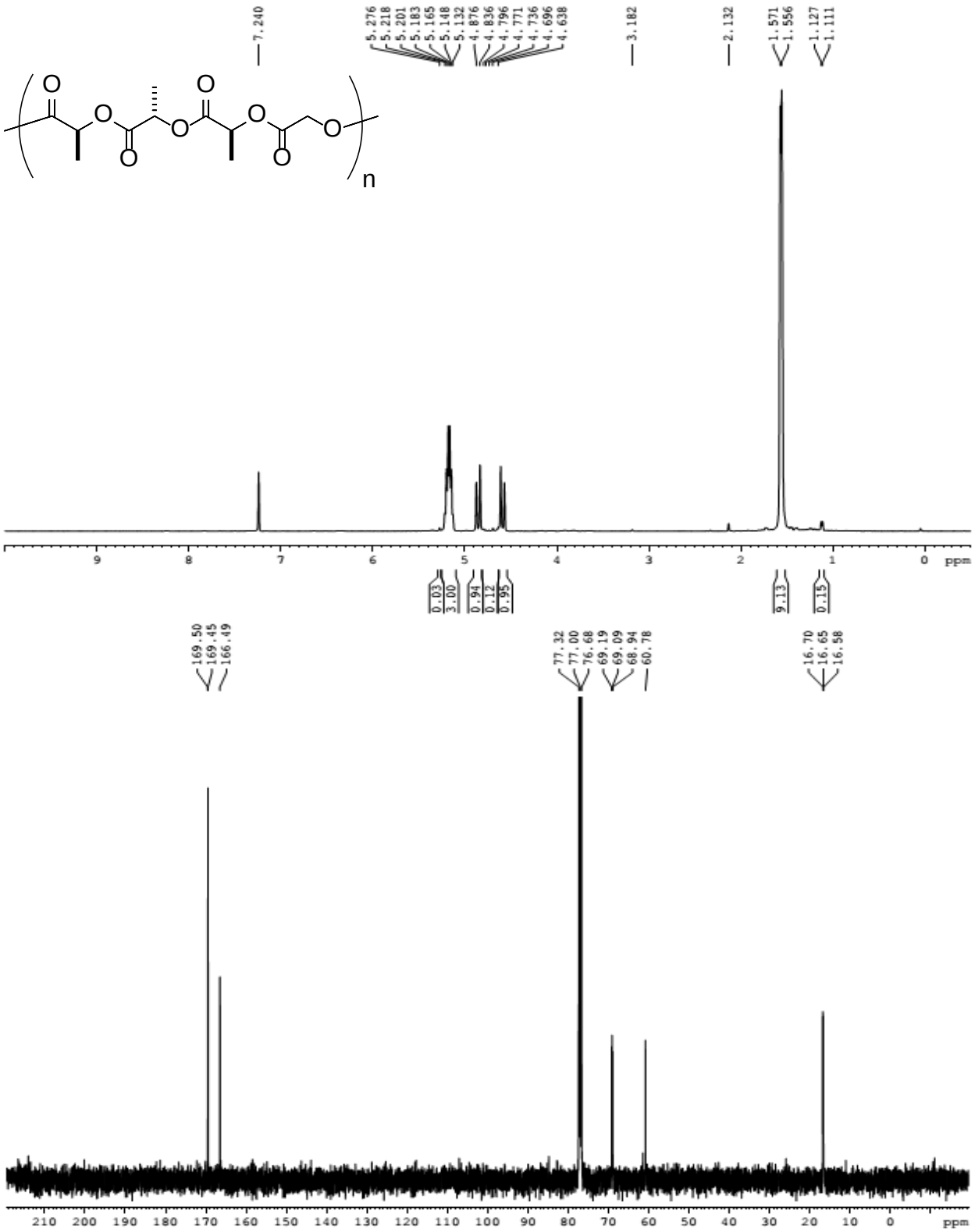


Figure 106. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly LLLG**. Prepared by Michael Washington.

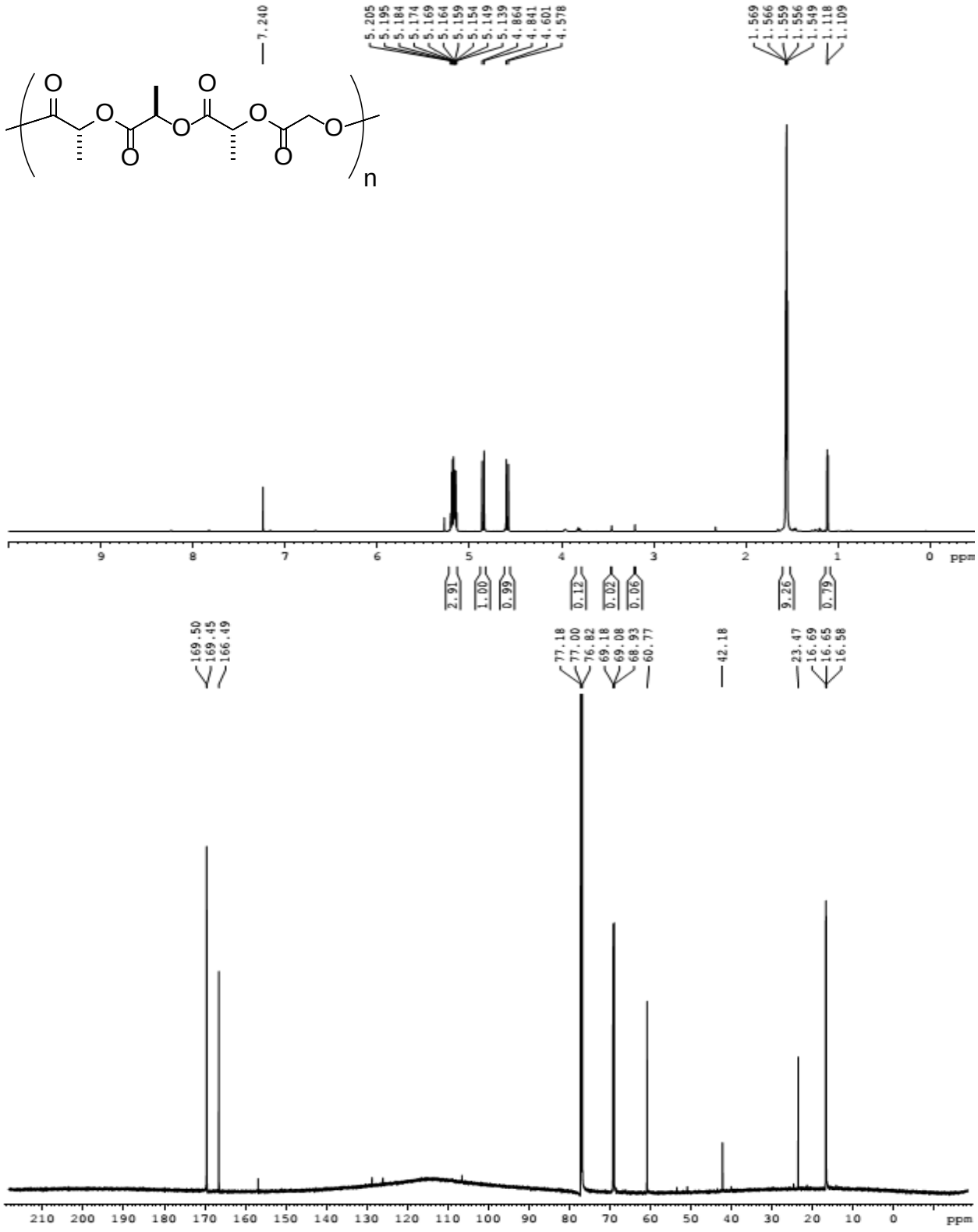


Figure 107. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly L$_R$L$_R$L$_R$G**.

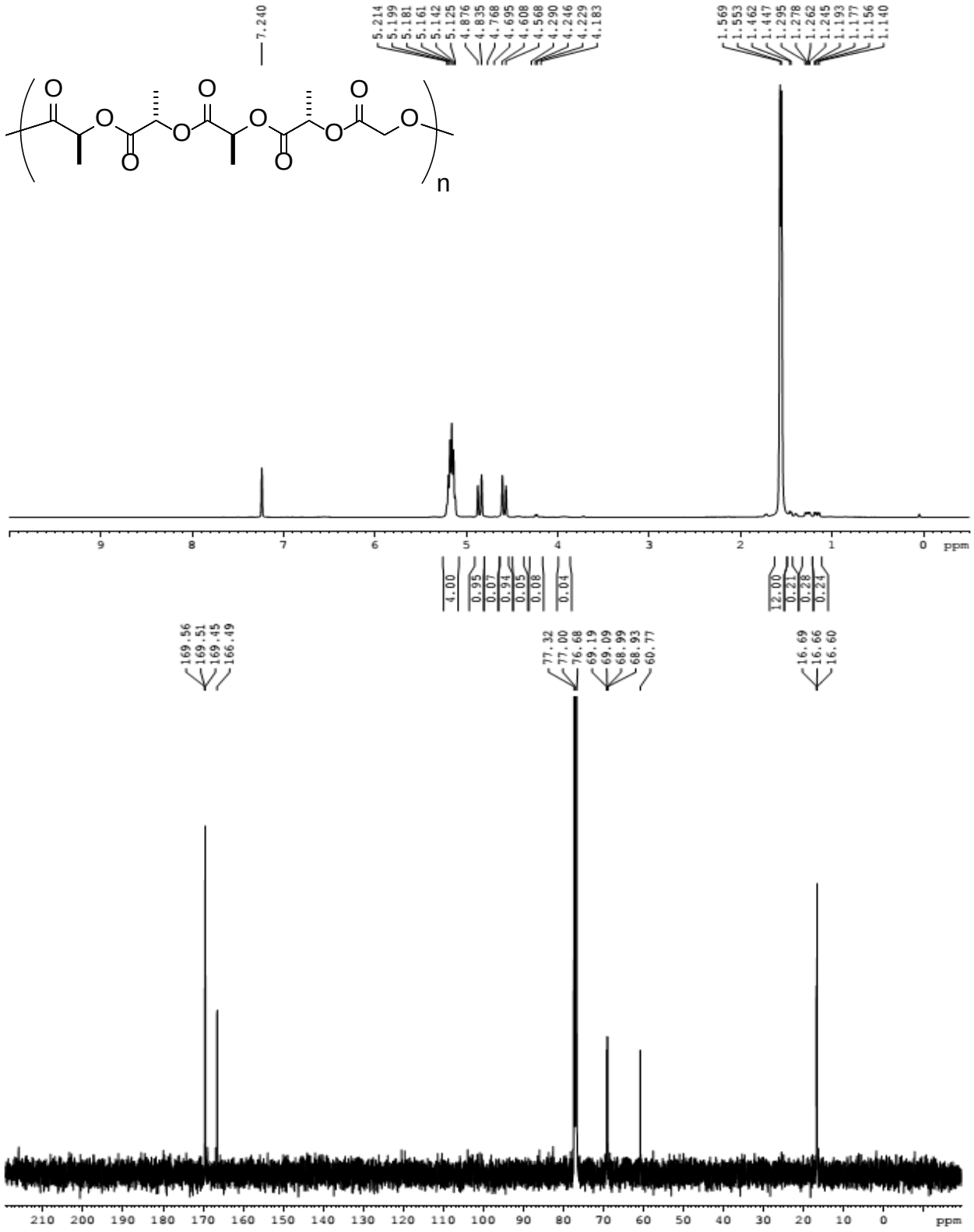


Figure 108. ^{1}H NMR (400 MHz, top) ^{13}C NMR (100 MHz, bottom) spectra of **Poly LLLLG**. Prepared by Michael Washington.

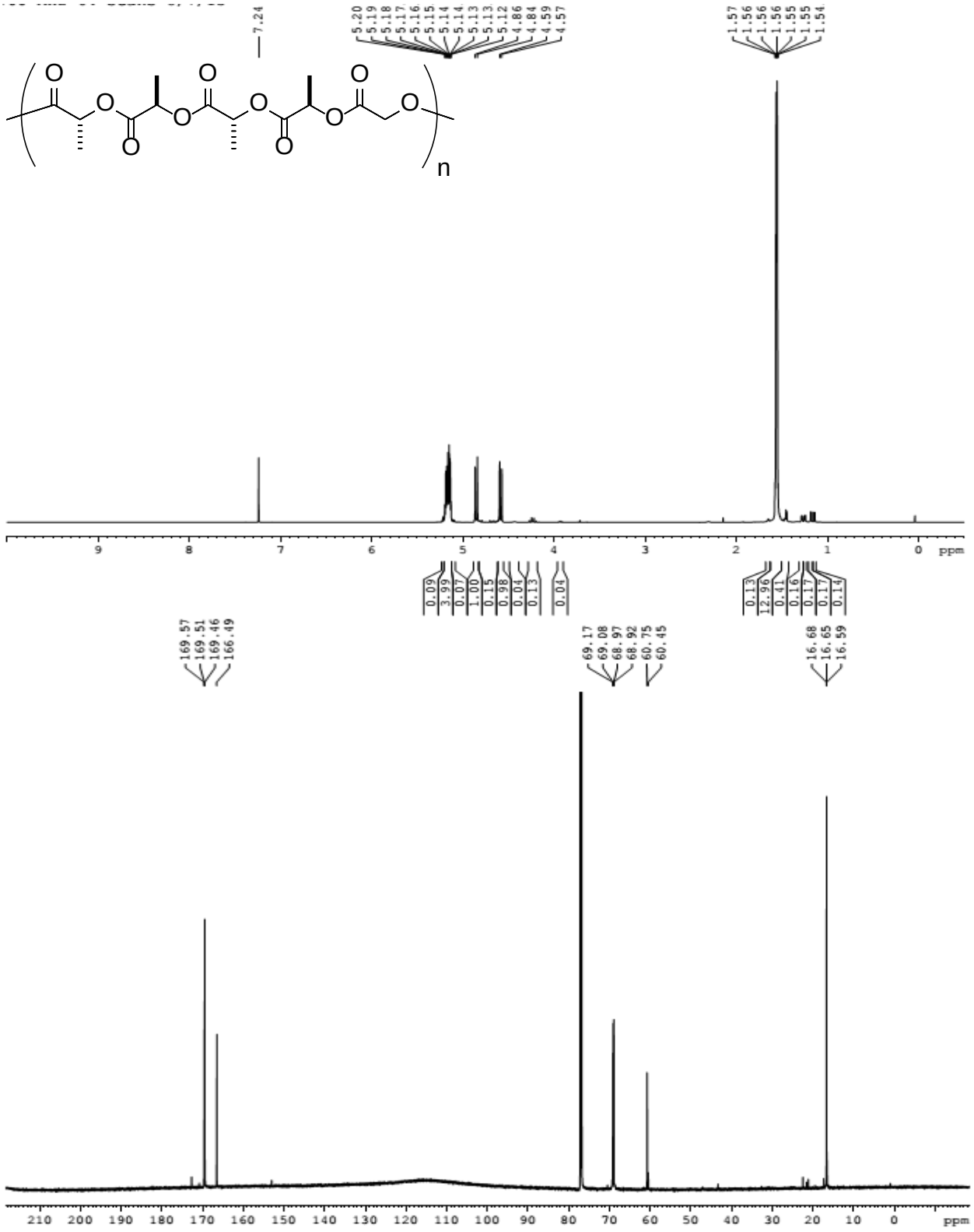


Figure 109. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly L$_R$L$_R$L$_R$L$_R$G**.

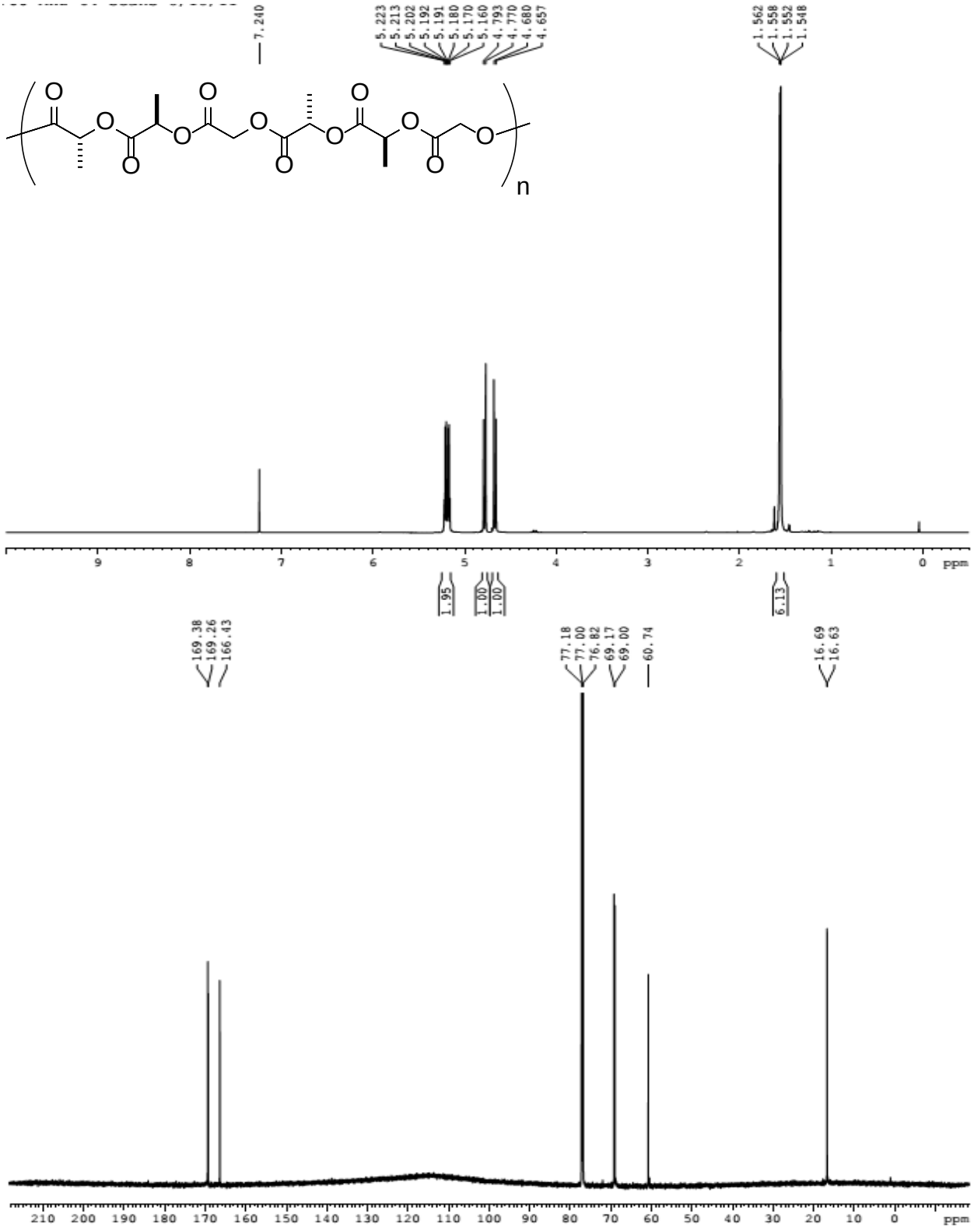


Figure 110. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly L$_R$L$_R$GLLG**.

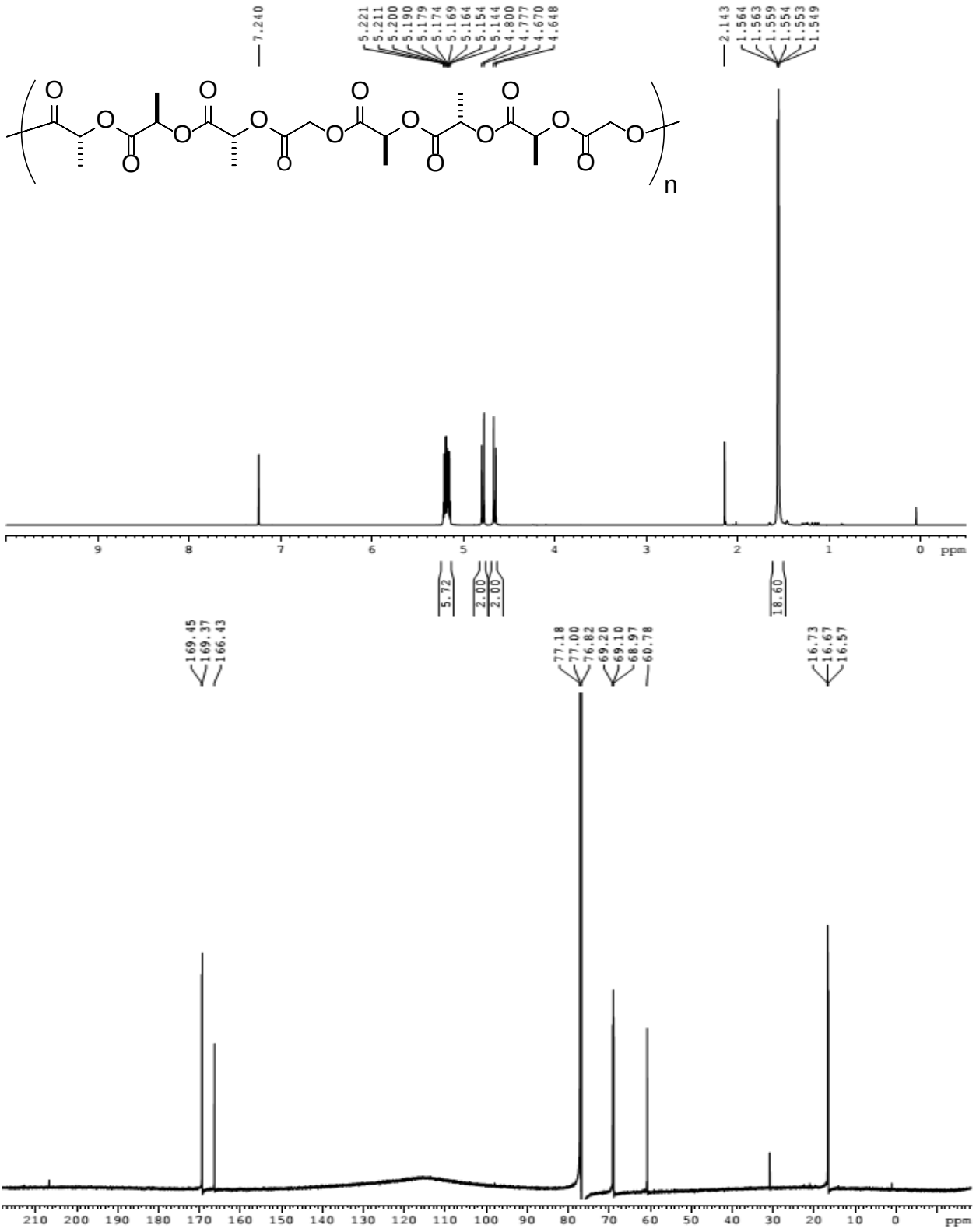


Figure 111. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly L$_R$L$_R$L$_R$GLLLG**.

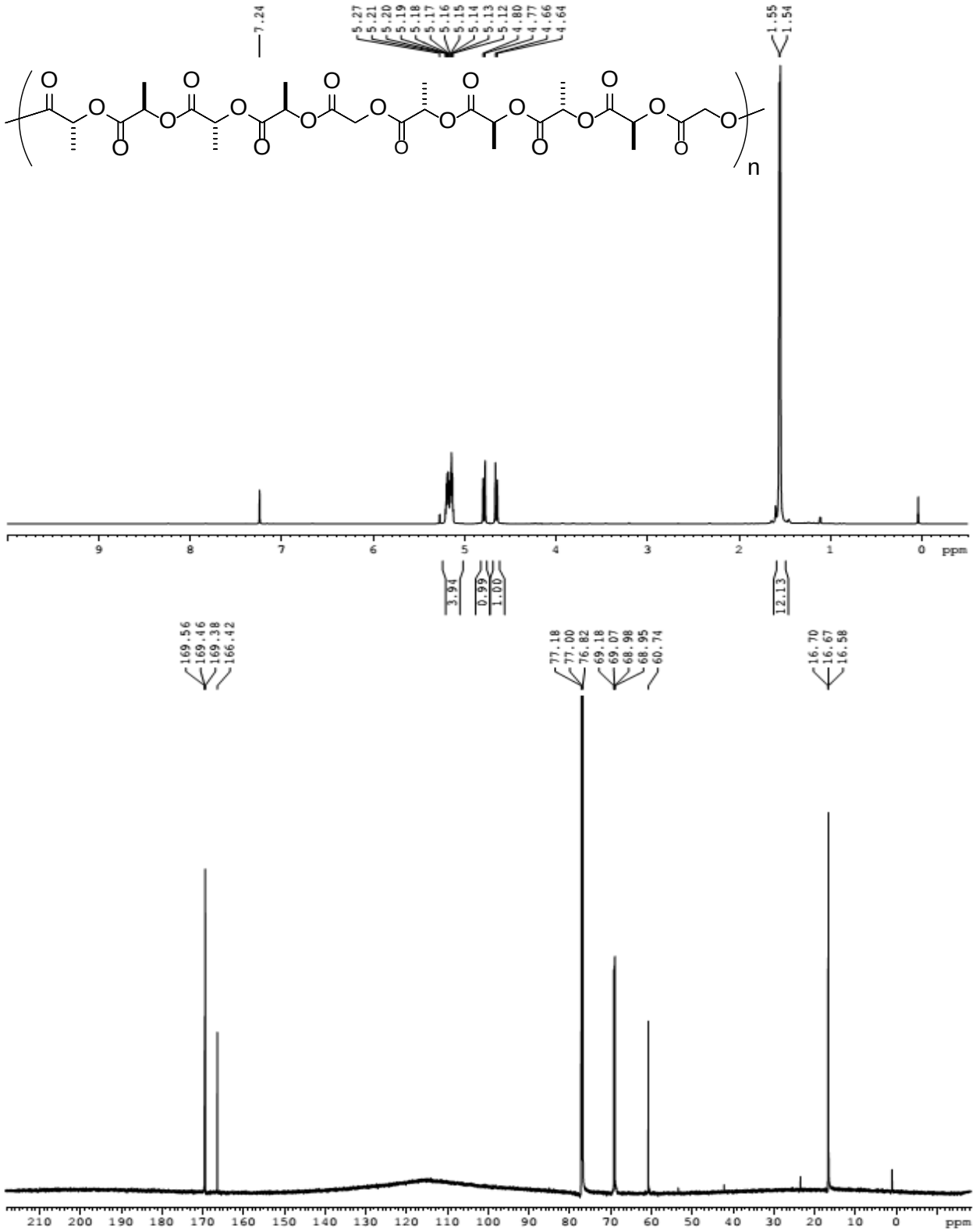


Figure 112. ^{1}H NMR (700 MHz, top) ^{13}C NMR (175 MHz, bottom) spectra of **Poly L*R*L*R*L*R*L*R*GLLLLG**.

A.4.1 SEC of polymers synthesized

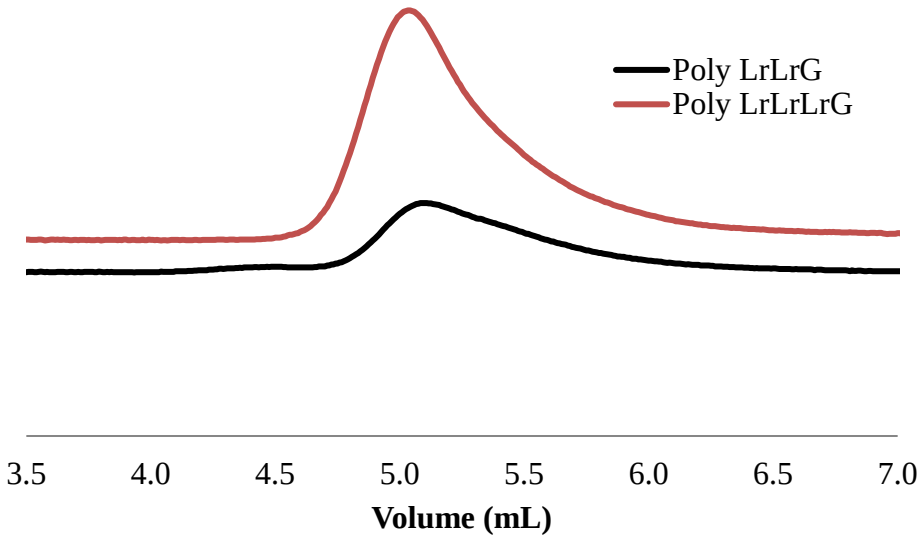


Figure 113. SEC (THF) of **Poly L$_R$L$_R$G** (black) and **Poly L$_R$L$_R$L$_R$G** (red) calibrated to PS standards.

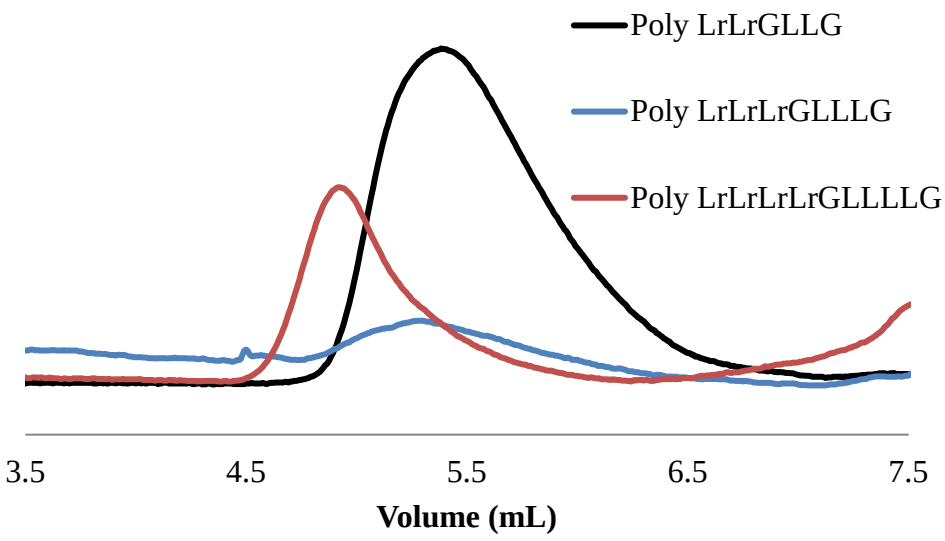


Figure 114. SEC (THF) of **Poly L$_R$L$_R$GLLG** (black), **Poly L$_R$L$_R$L$_R$GLLLG** (blue), and **Poly L$_R$L$_R$L$_R$L$_R$GLLLLG** (blue) calibrated to PS standards.

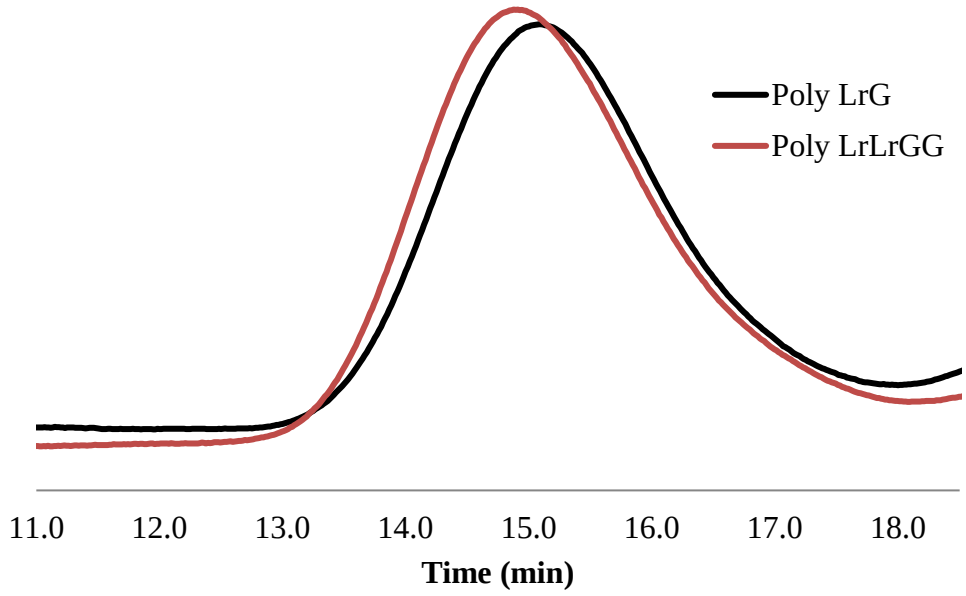


Figure 115. SEC (THF) of **Poly L*R*G** (black) and **Poly L*R*L*R*GG** calibrated to PS standards.

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